Cognitive Impairment Among HIV-positive Individuals in a Tertiary Infectious Disease Hospital in the Philippines

Joseree-Ann S. Catindig, MD,[1,2] *France Gil B. Rasay, MD,*[2] *Melmar C. Folloso, MD,*[2] *Rosario Jessica T. Abrenica, MD*[3]

ABSTRACT

Background: Disruption of neurocognitive functioning is one of the most frequent complications in patients infected with Human immunodeficiency virus. It manifests as a form of subcortical dementia characterized by psychomotor slowing, changes in mood and anxiety levels and deficits in memory, abstraction, information processing, verbal fluency, decision-making, and attention. The primary objective of this study is to determine the prevalence of neurocognitive impairment among HIV-positive individuals in the Philippines.

Methods: This is a cross-sectional study done at the outpatient department of a tertiary infectious disease hospital located in Manila, Philippines conducted from May to July 2015. The Montreal Cognitive Assessment – Filipino (MoCA-P) was used to differentiate non-cognitively impaired and cognitively impaired participants. Demographic data was obtained using structured interviews including the CD4 count.

Results: One hundred and twelve HIV positive patients were examined and 56.7% of them were noted to have cognitive impairment while none of them met the criteria for dementia. After logistics regression analysis, only the CD4 count (x=224) was shown to have significant association with cognitive impairment (p=0.0001, OR 0.96).

Conclusion: Cognitive impairment was significantly associated with low CD4 count, with a sensitivity of 100% for a count of <224. More than half or 58.7% of subjects with cognitive impairment did not show any neuropsychiatric symptoms. Neurocognitive impairment is still an important component of HIV infection and this study highlights the need to further increase awareness regarding this HIV complication.

Key words: cognitive impairment; HIV; dementia; HAND

INTRODUCTION

Human immunodeficiency virus (HIV) is a global concern causing a wide array of medical complications, which could affect the morbidity and mortality of the illness.

Despite advances in the treatment of HIV, the central nervous system (CNS) is still often affected by this disease. Impairment of cognition caused by HIV disease is known as HIV-associated neurocognitive disorder (HAND). Importantly, compared with

✉ Dr. Joseree-Ann S. Catindig
jscatindig@ust.edu.ph

[1] Department of Neuroscience and Behavioral Medicine, Faculty of Medicine and Surgery, University of Santo Tomas, Manila, Philippines

[2] Jose R. Reyes Memorial Medical Center, Manila, Philippines

[3] San Lazaro Hospital, Manila, Philippines

unaffected populations, HAND, even in its mild form, is associated with lower medication adherence, less ability to perform the most complex daily tasks, worse quality of life, difficulty obtaining employment, and shorter survival.[1]

Disruption of neurocognitive functioning is one of the most frequent complications in patients infected with HIV. It is estimated that 30% to 60% of HIV-positive individuals are affected.[2]

HAND manifests as subcortical dementia characterized by psychomotor slowing, changes in mood and anxiety levels and deficits in memory, abstraction, information processing, verbal fluency, decision-making, and attention.[3-5]

From 1984 to 2015, there were 25,684 HIV Ab sero-positive cases reported in the Philippines. In May 2015, there were 748 new HIV Ab sero-positive individuals confirmed by the STD/AIDS Cooperative Central Laboratory (SACCL).[6]

Here in the Philippines, to our knowledge there were no reports yet on the prevalence of cognitive impairment among HIV patients. The primary objective of this study was to determine the prevalence of neurocognitive impairment among HIV-positive individuals in the Philippines. Specifically, we would like to (1) Classify them as non-cognitively impaired, cognitively impaired, and dementia, (2) Determine the baseline demographics, education level, CD4 count, presence of family support, and (3) Assess the neuropsychiatric symptoms of our patients.

METHODOLOGY

This was a cross-sectional study done at the outpatient department of a tertiary infectious disease hospital located in Manila, Philippines conducted from May 2015 to July 2015 and approved by the Institutional Review Boards of the Jose R. Reyes Memorial Medical Center and San Lazaro Hospital. The following patients were included in the study: (1) patients with positive HIV status, (2) age 18 years old and above, (3) ability to comprehend study procedures, and able to provide informed consent. Patients with a diagnosis of severe psychiatric disorder (schizophrenia) and severely handicapped patients (loss of dominant hand, bilateral blindness, deafness) were excluded from the study.

Demographic data was obtained using structured interviews. The following data was collected: medical and psychiatric history, marital status; education, smoking, alcohol and illicit drug use, history of hypertension and diabetes, current medications, recent CD4 counts, and family support. Several tests were used to assess cognitive impairment, functional disability, and neuropsychiatric symptoms in all participants and are described in Table 1.

Montreal Cognitive Assessment – Filipino (MoCA-P) was used to differentiate non-cognitively impaired and cognitively impaired participants. The MoCA provides some coverage of executive function, motor skill, language fluency, and verbal learning. Barthel index and Lawton instrumental activities of daily living (IADL) scale was used to determine functional disability. Neuropsychiatric symptoms were assessed using the neuropsychiatric Inventory (NPI). The NPI has been used to characterize neuropsychiatric symptom profiles in a variety of neurological diseases.[7]

Data Processing and Statistical Analysis

Data were described using means and standard deviations, frequency counts and percentages. For bivariate analysis, t-test was used to analyze the difference between means of two groups, and one-way ANOVA for three or more groups. Fischer's exact test was used to determine the difference in frequencies between groups. Multivariate analysis was also done using binary logistic regression to determine independent factors of the outcome variable (cognitive impairment). For all tests, a 95% confidence level was considered significant ($p<0.05$). SPSS ver 19 was used as the statistical software. Accuracy parameters were determined using standard formulae.

RESULTS

We initially examined 112 HIV positive patients. The mean age of patients was 31.4 years and there was a preponderance of males. The mean year of formal education was 13.8 years. Majority of the patients were single, all with a history of alcohol intake, and majority were also smokers. Only one patient was found to have hypertension and no patient had diabetes. Mean duration of HIV was 24.4 months, mean duration of intake of medicines was 13.4 months, and mean CD4 count was 224.

The parameter used was MoCA–P, using the score of 26 as cut-off, majority (56.7%) of them were noted

Table 1. List of Neurocognitive and neuropsychologic tools applied in the present HIV study

Tools	Key features	Number of items	Time required	Maximum score	Cut off	Sensitivity and specificity/ reliability
Montreal cognitive assessment (MoCA)[8]	Cognitive screening tool for detection of MCI in primary care Addresses frontal/executive functioning	12 items	10 minutes	30	26 and above normal	Sensitivity of 90% for MCI 100% for mild dementia
Lawton Instrumental Activities of Daily Living (IADL) Scale[9]	Most useful for identifying how a person is functioning at the present time and for identifying improvement or deterioration over time.	8 items	5-15 minutes			Inter-rater reliability was established at 0.85
Barthel index	Measures performance in activities of daily living (ADL)	10 items	2-3 minutes	20	lower scores indicating increased disability	high inter-rater reliability (0.95) and test–retest reliability (0.89)
Neuropsychiatric Inventory (NPI) [10]	Assesses dementia-related behavioral symptoms which they felt other measures did not sufficiently address.	12 symptoms/ questions	5 minutes	frequency of symptoms: 4-point scale, 3-point scale, distress: 5-point scale		Inter-rater reliability ranged from 93.6% to 100%

to have cognitive impairment. All of our patients are independent in both basic and independent activities of daily living, hence none of them met the criteria for dementia. There was no sociodemographic and lifestyle variable that was significantly associated with presence/absence of cognitive impairment, as determined by MoCA–P. Duration of HIV, duration of intake of medicine and CD4 count, on the other hand, were significantly associated with cognitive impairment (see Table 2). Scores of those with impairment were significantly lower than in those without impairment for all components of MoCA, except for the "naming" and" orientation" domains, where the two groups achieved similar (high) scores (see Table 3).

All variables with p-value of <=0.500 were entered into a logistic regression model to determine the independent factors of cognitive impairment (see Table 4). The variables included were sex, years of formal education, history of smoking, HIV duration, CD4 count, and duration of medication intake. Results showed that only CD4 count was significantly associated with cognitive impairment (p=0.0001, O.R. 0.96). Since the coefficient was negative, it indicated an inverse relationship wherein lower CD4 counts, specifically less than 224 (average of the data set), were associated with the presence of cognitive impairment. Odds ratio was 0.96 which meant patients with cognitive impairment were 96% less likely to have CD4 counts >224 compared to those without cognitive impairment.

Neuropsychiatric inventory scale scores did not show significant association with cognitive impairment (see Table 5). Among those with cognitive impairment, 37 or 58.7% did not have any neuropsychiatric symptoms while 41.3% had. Among those with no cognitive impairment 32/48 or 66.7% showed neuropsychiatric symptoms.

DISCUSSION

From December 1986 when the first confirmed HIV patient in our country was identified, until now there are more than 25,000 HIV positive individuals.

Table 2. Comparison of sociodemographic and clinical characteristics of HIV patients with and without cognitive impairment as determined by MoCA-P (bivariate analysis).

	All	Without Impairment N=48	With Impairment N=63	P-value*
Sociodemographic				
Age in years, mean +/SD	31.4+/5.6	31.3+/5.7	31.4+/5.6	0.849
Sex				0.419
Male	105	44	51	
Female	6	4	2	
Years of formal education, mean +/SD	13.8+/2.2	13.5+/1.2	13.6+/0.84	0.305
Civil Status				0.619
Single	107	47	60	
Married	4	1	3	
Lifestyle				
Smoking				0.242
Yes	98	44	54	
No	13	4	9	
Alcoholic				
Yes	111	48	63	1.00
No	0	0	0	
Clinical				
+HPN	0	0	0	1.00
+DM	0	0	0	1.00
Duration of HIV in months, mean+/SD	24.4+/26.5	31.4+/27.5	19.1+/24.5	0.014
CD4 count, mean+/SD	224.1+/185.6	397.1+/141.3	92.3+/71.7	<0.0001
<200		0	61	<0.0001
Duration of med intake, in months, mean+/SD	13.4+/21.8	18.2+/25.5	9.5+/17.7	0.038
Type of meds taken				0.999
AZT	82	36	46	
TDF	7	3	4	
None	22	9	13	

**t-test* for independent samples for continuous variables and 2x2 Fischer's exact test for discrete variables.

Table 3. Components of MoCA-P, by presence/absence of cognitive impairment in the present HIV study.

	Without Impairment N=48	With impairment N=63	P-value
Executive (H=5, L=0)	4.9+/0.24	4.30+/0.91	<0.0001
Naming (H=3, L=0)	3+/0	3+/0	1.00
Attention (H=6, L=0)	5.6+/0.6	4.2+/0.74	<0.0001
Language (H=3, L=0)	2.0+/0.4	1.4+/0.6	<0.0001
Abstract (H=2, L=0)	1.6+/0.5	0.94+/0.6	<0.0001
Delayed Memory (H=5, L=0)	3.7+/0.6	1.9+/0.7	<0.0001
Orientation (H=6, L=0)	6.0+/0	6.0+/0	1.00

Table 4. Results of logistic regression with cognitive impairment as an outcome variable in the present HIV study (MoCA-P)

Variable	Coeff.	Std Err	P-value	O.R.	Low --	High
Sex	-1.4231	2.8547	0.6181	0.2410	0.0009	64.8495
education	0.7134	0.4579	0.1192	2.0410	0.8319	5.0072
smoker	-0.6850	1.4199	0.6295	0.5041	0.0312	8.1495
duration	-0.0251	0.0240	0.2944	0.9752	0.9304	1.0221
CD4	-0.0395	0.0099	0.0001	0.9612	0.9428	0.9800
duration of medications	0.0416	0.0364	0.2536	1.0425	0.9706	1.1196
Intercept	0.7794	6.3532	0.9024			

Table 5. NPI scores by presence/absence of cognitive impairment in the present HIV study

	0 N=69	1 N=20	2 N=12	3-4 N=10	P-VALUE
MOCA					0.323
(+)CI (<26) N=63	37 (58.7%)	14	5	7	
(-) MoCA N=48	32 (66.7%)	6	7	3	

The prevalence of cognitive impairment among HIV positive individuals is not yet been established. We are only dependent on statistics given by other countries. Recent publications estimate the prevalence of HAND exceeds 50%. This was somehow reflected in this pilot study. Sixty-three out of 112 patients (57%) were cognitively impaired using MoCA-P.

Previous studies, identified older age, low current CD4 count (<200), presence of past HIV-related CNS disease, longer HIV duration, low level of educational achievement, sex (female, as associated with lower socioeconomic status in some countries), neuropsychiatric disorders, eg, major depressive disorder, anxiety, posttraumatic stress disorder, psychosis, bipolar disorder (current or history of), current or history of illicit drug/alcohol abuse/ dependence as important risk factors in developing neurocognitive impairment in HIV patients.[11] In this study, only CD4 count was an independent factor associated with cognitive impairment. There was no sociodemographic and lifestyle variable that was significantly associated with the presence/absence of cognitive impairment, as determined by MoCA-P. NPI scores did not show significant association with cognitive impairment.

Reported cases of HIV associated cognitive impairment produced loss of retentive memory, impaired attention, lack of visuospatial memory, difficulty with complex sequencing, and mental slowing.[12,13] Our results showed that scores of those with cognitive impairment were significantly lower than in those without impairment for visuospatial memory, executive functioning, retentive memory, attention, language, and abstraction.

In our study we also tried to group patients based on the current type of anti-retroviral drugs they were taking, since the drug zidovudine was proven to be effective in improving cognitive performance.[14] However, in our results, the type of medication was not associated with presence or absence of cognitive impairment, provided that majority of our patients were taking zidovudine as one of their anti-retroviral medications.

As previously mentioned, cognitive impairment among HIV positive individuals was associated with lower medication adherence, worse quality of life, and shorter survival, hence screening all HIV positive patients, particularly with low CD4 count should be started as a routine in our country, as to what the recent international consensus emphasized. Furthermore, because the CNS is commonly one of the first targets of HIV infection, good practice suggests that a patient's neurocognitive profile should be assessed early (within 6 months of diagnosis, as soon as clinically appropriate) using

a sensitive screening tool.[15] Newer studies show the Montreal Assessment Scale (Montreal Cognitive Assessment), like what we used in this study has an advantage in that it is free and evaluates multiple cognitive domains in one sitting.[16] If possible, screening should take place before the initiation of Antiretroviral Therapy, as this will establish accurate baseline data and allow for subsequent changes to be more accurately assessed. This study has several limitations. The study was conducted in an urban outpatient HIV center which may not be representative of HIV-positive individuals in the community and rural settings. This study did not discuss regarding treatment guidelines on HAND.

CONCLUSION

More than half or 56.7% of subjects with HIV in this study met the criteria for neurocognitive impairment with the MoCA-P, despite the fact that almost all were treated with anti-retroviral drugs. Cognitive impairment was significantly associated with low CD4 count, with a sensitivity of 100% for a count of <224. More than half or 58.7% of subjects with cognitive impairment did not show any neuropsychiatric symptoms. Our results, while admittedly tentative, and still ongoing, indicate that neurocognitive impairment was likely to be an important component of HIV infection and highlighted the need to further increase awareness regarding this HIV complication.

Declaration of Competing Interests

The authors declare that there are no conflicts of interest and no source of funding for this study.

Acknowledgments

The authors acknowledge Dr. Simeon Marasigan for his contribution in the conceptualization and final editing of this study. May he continue to inspire residents and young neurologists to dedicate their life in helping patients with dementia as what he has done throughout his life. To him we dedicate this manuscript.

REFERENCES

1. Mind Exchange Working Group. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. *Clin Infect Dis* [Internet]. 2013;56(7):1004–17. Available from: http://dx.doi.org/10.1093/cid/cis975
2. Grant I. Neurocognitive disturbances in HIV. *Int Rev Psychiatry* [Internet]. 2008;20(1):33–47. Available from: http://dx.doi.org/10.1080/09540260701877894
3. Spudich S, González-Scarano F. HIV-1-related central nervous system disease: current issues in pathogenesis, diagnosis, and treatment. *Cold Spring Harb Perspect Med* [Internet]. 2012;2(6):a007120. Available from: http://dx.doi.org/10.1101/cshperspect.a007120
4. González-Scarano F, Martín-García J. The neuropathogenesis of AIDS. *Nat Rev Immunol* [Internet]. 2005;5(1):69–81. Available from: http://dx.doi.org/10.1038/nri1527
5. Portegies P, Enting RH, de Gans J, Algra PR, Derix MM, Lange JM, et al. Presentation and course of AIDS dementia complex: 10 years of follow-up in Amsterdam, The Netherlands. *AIDS*. 1993;7(5):669–75.
6. STD/AIDS Cooperative Central Laboratory (SACCL) October 2013.
7. McArthur JC. HIV dementia: an evolving disease. *J Neuroimmunol* [Internet]. 2004;157(1–2):3–10. Available from: http://dx.doi.org/10.1016/j.jneuroim.2004.08.042
8. Galvin JE, Sadowsky CH, NINCDS-ADRDA. Practical guidelines for the recognition and diagnosis of dementia. *J Am Board Fam Med* [Internet]. 2012;25(3):367–82. Available from: http://dx.doi.org/10.3122/jabfm.2012.03.100181
9. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969 Autumn;9(3):179–86.
10. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* [Internet]. 1997;48(5 Suppl 6):S10-6. Available from: http://dx.doi.org/10.1212/wnl.48.5_suppl_6.10s
11. Mind Exchange Working Group. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. *Clin Infect Dis* [Internet]. 2013;56(7):1004–17. Available from: http://dx.doi.org/10.1093/cid/cis975
12. Neurologic Complications of HIV and Antiretroviral therapy, Duarte et al., the PRN notebook October 200, published in New York City by the Physicians Res Our reach network Inc.
13. Ropper A, Samuels M, Klein J. Adams and Victor's Principles of Neurology. 10th ed. New York, NY: McGraw-Hill Medical; 2014.
14. Sidtis JJ, Gatsonis C, Price RW, Singer EJ, Collier AC, Richman DD, et al. Zidovudine treatment of the AIDS dementia complex: Results of a placebo-controlled trial. *Ann Neurol* [Internet]. 1993;33(4):343–9. Available from: http://dx.doi.org/10.1002/ana.410330403
15. Valcour V, Paul R, Chiao S, Wendelken LA, Miller B. Screening for cognitive impairment in human immunodeficiency virus. *Clin Infect Dis* [Internet]. 2011;53(8):836–42. Available from: http://dx.doi.org/10.1093/cid/cir524
16. Watkins C, Treisman G. Cognitive impairment in patients with AIDS – prevalence and severity. *HIV AIDS (Auckl)* [Internet]. 2015;35. Available from: http://dx.doi.org/10.2147/hiv.s39665