

Risk Factors for Neurocognitive Impairment in HIV-Infected Patients

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Abstract: *Depression in people living with HIV (PLWH) has become an urgent issue and has attracted the attention of both physicians and epidemiologists. Currently, 39% of HIV patients are reported to suffer from depression. This population is more likely to experience worsening disease states and, thus, poorer health outcomes. In this study, we analyzed research growth and current understandings of depression among HIV-infected individuals. Research landscapes related to this research field include risk behaviors and attributable causes of depression in HIV population, effects of depression on health outcomes of PLWH, and interventions and health services for these particular subjects. We identified a lack of empirical studies in countries where PLWH face a high risk of depression, and a modest level of interest in biomedical research. By demonstrating these research patterns, highlighting the research gaps and putting forward implications, this study provides a basis for future studies and interventions in addressing the critical issue of HIV epidemics.*

Keywords: HIV, dementia, International HIV Dementia Scale.

1. Introduction

The central nervous system (CNS) is a major target for HIV infection with high viral loads often observed in cerebrospinal fluid and in different anatomical sites such as the caudate nucleus and the hippocampus of HIV-infected patients. [1] In the CNS, HIV infects and replicates on macrophages, microglia and multicellular glia, resulting in the release of neurotoxic factors and subsequent cell damage. [2] In 1991, the American Academy of Neurology divided HIV-associated neurocognitive disease (HAND) into two different categories: HIV-associated dementia (HAD) and mild neurocognitive disorder. HAD is characterized by impairment in multiple domains, particularly learning of new information, information processing, and attention or concentration, that impact at least two activities of daily living and result in at least one functional or psychosocial change. In mild neurocognitive disorder, there is a reduction in mental accuracy with loss of efficiency at work and reduced performance on domestic tasks,¹ but with a much lower impact on activities of daily living.

A decade later, Antinori et al., [3] introduced a new category of asymptomatic neurocognitive disorders based on the finding that some individuals have subclinical impairment on neurocognitive evaluation without any impact on activities of daily living. Prevalences of asymptomatic neurocognitive disorder (ANA), mild neurocognitive disorder and HAD are 30–35%, 20–25% and 2–3%, respectively.⁴ CD4⁺ cell counts lower than 200 cells/mm³, age greater than 50 years and low educational status were found to be risk factors for HIV-associated neurocognitive disorders (HAND). [4] The gold standard for diagnosing neurocognitive impairment is a battery of neuropsychological tests applied by a trained neuropsychologist. However, such comprehensive assessment is not feasible in daily clinical practice and simpler screening tools are needed. [4,5] The IHDS is a rapid assessment tool that evaluates memory-recall and both

motor and psychomotor speed. [5,6] It consists of three subtests: [1] timed finger tapping which measures motor speed; [2] timed alternating hand sequence test which assesses psychomotor speed; and [3] recall of 4 words (blue, dog, hat and apple) at 2 minutes which assesses memory registration and recall. Each of these tests is rated on a scale of 0–4 and the maximum possible score on the IHDS is 12. Validation of the IHDS in Brazil was conducted by Rodrigues et al., [5] and showed sensitivity and specificity for detecting HAND of 55% and 80%, respectively. A moderate-to-high interobserver agreement was observed and a there was reasonable agreement between the IHDS and other neuropsychological tests. [5] Another neurocognitive assessment tool is the Mini- Mental State Examination (MMSE) that evaluates orientation, attention and calculation, registration, recall, language and the ability to follow simple commands. [7] However, the MMSE was originally developed to screen for cortical dementia such as Alzheimer’s disease and there might be limitations on its use to assess subcortical disorders, such as those observed among HIV-infected patients. [7]

A self-perception questionnaire was recently proposed by the European AIDS Clinical Society as a first step in neurocognitive evaluation of HIV-infected patients. [9] The questionnaire has three items related to memory, attention and information processing, based on a previous study conducted by Simioni et al. [8] However, the performance of the questionnaire in clinical setting has not been systematically evaluated. The aim of this study was to evaluate the factors associated with performance on the IHDS and MMSE and level of agreement between scores on these screening tools and patients’ self-perception of neurocognitive status.

2. Material and Methods

Between October 2015 and February 2018, 63 consecutive HIV-infected patients were recruited for the study at Service of Infectious Disease, University Hospital Centre “Mother

Tirana, Albania. All patients included were adults and had confirmed HIV diagnosis. Patients were excluded if they were illiterate, had severe psychiatric conditions or current CNS opportunistic infection. Sociodemographic, clinical and laboratory data were obtained through chart review and patient interview. Neurocognitive evaluation using validated versions of the IHDS5 and MMSE7 was conducted by trained researchers. For the IHDS, a score less than or equal to 10 was considered to be altered, based on the study of Rodrigues et al. that showed a sensitivity and specificity for detection of HAND of 55% and 80%, respectively. [5] For the MMSE, a cut-off score based on years of education was used as following: 18 points for patients with four years of education or less and 26 points for those with more than four years of education. [7] Cognitive self-perception was assessed by a questionnaire recommended by the European AIDS Clinical Society guideline. [8,9] The questionnaire includes three items: [1] "Do you experience frequent memory loss?"; [2] "Do you feel that you are slower when reasoning, planning activities or solving problems?"; [3] "Do you have difficulties paying attention?". For each of the questions, patients must choose one of the following answers: [a] never, [b] hardly ever or [c] yes, definitely. The EACS guideline recommends that patients be submitted to a more thorough neurocognitive evaluation if the response on at least one of the items is "yes, definitely". Patients' depressive symptoms were assessed using the Beck Depression Inventory (BDI),¹⁰ a self-rated 21-item questionnaire validated in Brazil by Gorenstein and Andrade.¹¹ A score of < 14 suggests the presence of no or minimal depressive symptoms while scores from 14–19, 20–28 and 29–63 are suggestive of the presence of mild, moderate or severe depressive symptoms, respectively. Demographic information, CD4+ cell count, HIV viral load, antiretroviral regimen, smoking history, use of illicit drugs and alcohol abuse were obtained from patients' medical records. Descriptive analysis of frequency and proportions were used for categorical variables. Comparison of proportions was conducted using Pearson's Chi-square test. Means and standard deviation were used for normally distributed continuous variables. Statistical significance was set up at 0.05. The Medcalc statistical package (Version 18.0) was used to conduct all analyses.

3. Results

Sixty-three patients were assessed throughout the study period. Among the patients included, 45 (71.4%) were male, with a mean age of 42.9 years (range 19.0–73.0), 39 (61.9%) individuals were non-white and 38 (60.3%) had eight or less years of education. Only two patients (3.2%) had a CD4+ count less than 200 cells/mm³. Fifty-eight patients were on antiretroviral therapy (ART) and 30 (51.7%) of these were using efavirenz. Among the forty-four patients that had been on ART for more than 24 weeks, 37 (84.1%) had undetectable viral load. Twenty-four (33.9%) patients showed symptoms of depression, where most of these were suggestive of mild depression. Neurocognitive assessment showed that 34 (54.0%) patients had low performance (<11) on the IHDS and scores were inversely associated with age (OR=0.13; 95%CI 0.02-0.67). Performance on the IHDS was not significantly associated with efavirenz use, gender, CD4+ cell count; viral load or depressive symptoms. None

of the patients included had an MMSE score below the cut-off level. Regarding the self-assessment questionnaire, 25.7% of the patients answered positively for at least one of the questions. Among those patients self-reporting no problems, 42.1% had low performance on the IHDS.

4. Discussion

A high proportion of HIV-infected patients were found to have impaired performance on the IHDS. A similar high prevalence of HAND, as suggested by low scores on the IHDS, was also reported by Oshinaike et al. in Nigeria¹² and Rodrigues et al. in Brazil. [5] With the introduction of highly-active antiretroviral therapy (HAART), a reduction in the incidence of HAND was observed but its prevalence has increased due to improved patient survival. [5,10] Currently, as the HIV population is becoming older, both incidence and prevalence of HAND appear to be increasing.¹³ Indeed, we have found age to be associated with performance on the IHDS - a finding also reported by others. [14,15] We failed to find an association between CD4+ cell count and performance on the IHDS, such as the associations found by Antinori et al. [3] However, the number of patients with CD4+ cell count less than 200 cells/mm³ in the present study was too small to make meaningful comparisons. Efavirenz is associated with a variety of psychiatric and neurological conditions due to its neurotoxicity. [16] However, we found no association between efavirenz use and performance on the IHDS, in agreement with the results of Lopardo et al. [16-18] Depression is frequent among HIV-infected patients. Kagee & Martin conducted a study in South Africa using BDI and estimated a prevalence of moderate and severe depression of 37.4% and 20%, respectively. Simioni et al., [8] (also reported a high prevalence of HAND among HIV-infected patients with long-standing undetectable viral load without neurocognitive complaints. Misdiagnosis of HAND can have a significant impact on HIV care. HAND overdiagnosis might reduce patients' self-esteem, lead to inappropriate medical interventions and increases the already high cost of AIDS treatment.¹⁸ Conversely, lack of early diagnosis might delay appropriate interventions such as antiretroviral therapy modifications. [19]

5. Conclusion

Along with the significant increase of scientific literature volume, depression among HIV-infected patients has been extensively examined. Research landscapes related to this field include risk behaviors and attributable causes of depression in HIV population, effects of depression on health outcomes of PLWH, and interventions and health services for these particular subjects. Most of the existing interventions are focused on reduction of risk behaviors and social stigma, rather than interventions that target the infected populations. Since HIV is regarded as an incurable infection, it is essential to prevent incident HIV infections and the reduction of unprotected sex, injecting drugs, or substance abuse would lighten the global burden of HIV epidemic. Additionally, stigma and discrimination, either perceived or self-stigma, is responsible for depressive symptoms in the majority of HIV-infected individuals. Therefore, interventions addressing these problems would

effectively lower the prevalence of HIV infection, in general, and depression among PLWH in particular. Although the field of depression in PLWH has been extensively studied, biomedical aspects of this research topic deserve more attention, since such research topics as viral load or immune responses currently hold relatively low positions. In addition to psychological and somatic symptoms, biological factors also contribute to depression among HIV patients. A number of studies have recognized that chronic viral infections, including HIV, are able to affect immune system and influence the way the central nervous system mediates psychological status, resulting in neuropsychiatric consequences. Biologically, HIV may trigger the release of inflammatory cytokines and induce sickness behaviors that are similar to depressive symptoms. Additionally, while many antidepressants relieve the symptoms by elevating the level of a neurotransmitter called serotonin, HIV is capable of altering the precursor (tryptophan) and, thus, suppress the efficacy of the medications to a certain extent. Evidences of neuronal damages have been recorded only a year after HIV infections and it been has reported that the use of antiviral therapies and the stage of the disease are associated with worsening depression.

References

- [1] Christo PP. Alterações cognitivas na infecção pelo HIV e AIDS. *Rev Assoc Med Bras* 2010;56:242-247.
- [2] Valcour V, Sithinamsuwan P, Letendre S, Ances B. Pathogenesis of HIV in the central nervous system. *Curr HIV/AIDS Rep* 2011;8:54-61.
- [3] Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007;69:1789-1799.
- [4] Zipursky AR, Gogolishvili D, Rueda S, et al. Evaluation of brief screening tools for neurocognitive impairment in HIV/AIDS: a systematic review of the literature. *AIDS* 2013;27:2385-2401.
- [5] Rodrigues RA, Oliveira RL, Grinsztejn B, Silva MTT. Validity of the International HIV dementia scale in Brazil. *Arq Neuropsiquiatr* 2013;71:376-379.
- [6] Sacktor NC, Wong M, Nakasujja N, et al. The International HIV Dementia Scale: a new rapid screening test for HIV dementia. *AIDS* 2005;19: 1367-1374.
- [7] Brucki, SM, Nitrini, R, Caramelli, P, Bertolucci, PH, Okamoto, IH. Sugestões para o uso do mini-exame do estado mental no Brasil. *Arq Neuropsiquiatr* 2013;61:777-81.
- [8] Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS* 2010;24: 1243-1250.
- [9] EACS - European AIDS Clinical Society. Guideline version 8.0 October 2015. Available at: http://www.eacsociety.org/files/2015_eacsguidelines_8.0-english_rev-20151221.pdf. Accessed on October 30, 2015.
- [10] Beck AT, Ward C, Mendelson M. Beck depression inventory (BDI). *Arch Gen Psychiatry* 1961;4:561-571.
- [11] Gorenstein, C, Andrade, LHSG. Validation of a Portuguese version of the Beck Depression Inventory and the State-Trait Anxiety Inventory in Brazilian subjects. *Brazilian journal of medical and biological research. Rev Bras Pesq Med Biol* 1996;29:453-457.
- [12] Oshinaike OO, Akinbami AA, Ojo OO, Ojini IF, Okubadejo UN, Danesi AM. Comparison of the Minimental State Examination Scale and the International HIV Dementia Scale in Assessing Cognitive Function in Nigerian HIV Patients on Antiretroviral Therapy. *AIDS Res Treat* 2012; 1:1-6.
- [13] Pacheco Filho, JR, Santos, FH. Estudos brasileiros sobre demência associada ao HIV. *J Bras Doenças Sex Transm* 2008;20:196-203.
- [14] Mossie, TB, Tegegne, MT. HIV dementia among HIV positive people at Debre markos hospital, Northwest Ethiopia. *Am J Psychol Neurosci* 2014;2:18-24.
- [15] Lopardo GD, Bissio E, Del C Iannella M, Crespo AD, Garone DB, Cassetti LI. Good neurocognitive performance measured by the international HIV dementia scale in early HIV-1 infection. *J Acquir Immune Defic Syndr* 2009;52:488-492.
- [16] Ciccarelli N, Fabbiani M, Di Giambenedetto S, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology* 2011; 76:1403-1409.
- [17] Kagee A, Martin L. Symptoms of depression and anxiety among a sample of South African patients living with HIV. *AIDS Care* 2010; 22: 159-165.
- [18] Nunn AS, Fonseca EM, Bastos FI, Gruskin S. AIDS Treatment in Brazil: Impacts And Challenges. *Health Affairs* 2009; 28:1103-1113.
- [19] Mind Exchange Working Group. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. *Clin Infect Dis.* 2013;56:1004-1117