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Association Between Frailty and HIV-Associated Neurodegenerative Disorders Among Older Adults Living with HIV

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Abstract

The population of aging adults living with human immunodeficiency virus (HIV) is growing worldwide and evidence suggests that frailty occurs prematurely among them. In turn, frailty has been associated with cognitive decline. It is unknown, however, if people with both frailty and HIV infection have a higher risk of cognitive impairment compared with nonfrail HIV-infected persons. Therefore, the main objective of this study was to determine the association between the phenotype of frailty and HIV-associated neurocognitive disorders (HAND) among adults aged 50 years or older living with HIV/AIDS. A cross-sectional study was conducted on 206 adults living with HIV receiving care in a university-affiliated tertiary care hospital in Mexico City. Frailty was defined as per the Fried criteria. The presence of HAND was established according to the Antinori criteria: HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), or cognitively nonimpaired. Multinomial logistic regression models were used to test the independent association between frailty and HAND adjusting for potential confounders. Mean age of participants was 60.5 ± 6.3 years and 84.9% were male. Prevalence of HAND and frailty phenotype was 66.0% and 2.9%, respectively. The unadjusted analysis showed that both prefrail and frail statuses were associated with MND but not with ANI. However, after adjustment, the association with MND remained significant only among prefrail participants and no longer for frail persons (risk ratio [RR] = 5.7, 95% confidence intervals [CI] 1.09–29.82; $p = .039$ and RR = 18.3, 95% CI 0.93–362.6; $p = .056$, respectively). Prefrailty is associated with symptomatic neurocognitive disorders in older adults living with HIV. The spectrum of the frailty phenotype in this already vulnerable population should serve as an indicator of concomitant cognitive decline.

Keywords: cognitive impairment, frailty, HIV-associated neurocognitive disorders

Introduction

The population of older people living with human immunodeficiency virus (PLWHIV) infection is growing worldwide.[1] HIV-infected adults face the onset of geriatric syndromes roughly 15 years earlier than noninfected adults.[2] The possible negative synergistic effect of the HIV infection and the aging process may be the result of a common biological mechanism that includes a sustained inflammatory response.[3] In turn, this can have deleterious effects on the health of older individuals. On the contrary, premature non-AIDS-related comorbidities such as cardiovascular disease, hypertension, renal failure, diabetes, frailty, or cognitive impairment may worsen health-related outcomes of aging PLWHIV in the highly active antiretroviral therapy (HAART) era.[4,5]

Aging is the most important risk factor for cognitive decline and, in the same vein, frail persons have an increased risk of cognitive impairment. Frailty is a major risk factor of incident dementia, particularly vascular dementia,[6] where atherosclerosis could partially explain its development. However, it remains elusive whether early onset of frailty in PLWHIV could also increase the risk of cognitive decline

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in this population. If so, this knowledge could prompt clinicians to develop early interventions on the appearance of features of the frailty phenotype to prevent subsequent complications associated with cognitive impairment. Hence, the main objective of this study is to determine the association between frailty and HIV-associated neurocognitive disorders (HAND) among PLWHIV. Our hypothesis is that in PLWHIV, HAND occur more frequently among prefrail and frail participants in comparison with those who do not meet the frailty criteria.

Materials and Methods

Study population

This is a cross-sectional study. Eligible participants were individuals with documented HIV infection aged 50 years or older receiving ambulatory care at the HIV clinic of a university-affiliated tertiary care center in Mexico City. Participants were identified through the HIV/AIDS clinic database and clinic appointment schedules/records between August 2014 and August 2016. Participants underwent a comprehensive geriatric assessment by trained staff using standardized methods. Exclusion criteria included conditions that may be mistakenly classified as physical frailty, such as amputation of upper and/or lower limb; severe dementia; class III–IV heart failure by the New York Heart Association functional classification[7]; class III–IV chronic obstructive pulmonary disease according to the Global Initiative for Chronic Obstructive Lung Disease classification[8]; stage III–IV rheumatoid arthritis according to the American College of Rheumatology classification[9]; stage 4–5 Parkinson's disease according to the Hoehn and Yahr scale[10]; as well as patients with a history of ischemic and/or embolic cerebrovascular disease with motor sequelae, and myocardial ischemia in the previous 3 months. All participants provided written informed consent. The study was approved by the institutional research ethics committee.

Definition of frailty

Frailty was defined according to the phenotype proposed by Fried *et al.*,[11] which has been previously validated in a Mexican population[12]: (1) weight loss was defined as self-report of unintentional loss of >10 lb within the previous year; (2) self-reported exhaustion was defined using two questions from the Center for Epidemiological Studies-Depression (CES-D) scale[13]; (3) slowness was determined using the 4-m gait speed test adjusted for sex and height; (4) weakness was established when there was decreased dynamometer-measured hand-grip strength adjusted for sex and body mass index (BMI); and (5) low physical activity was determined using the Spanish version of the Physical Activity Scale for the Elderly,[14] where participants who were in the lowest sex-adjusted quintile were categorized as positive for this frailty criterion. As recommended, participants meeting three or more criteria were classified as frail, one or two as prefrail, and those meeting none as nonfrail.

HIV-associated neurocognitive disorders

HAND presence and classification were determined as proposed by Antinori *et al.*[15] and three categories were established: HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and cognitively nonimpaired. All participants underwent neuropsychological assessment by trained personnel. For this purpose, the NEUROPSI neuropsychological battery was administered.[16] This test succinctly assesses a wide spectrum of cognitive domains, including orientation, attention/concentration, memory, language, visuospatial abilities, and executive functions. The NEUROPSI includes items that are relevant for Spanish-speaking communities (language and picture tests that have high, medium, and low frequency of occurrence in the Spanish language). It can be applied to illiterates and individuals with a low educational level. Administration time ranges from 25 to 30 min. Normative data for grading the test stem from validations performed in Mexicans and are adjusted according to age and educational level. The NEUROPSI has shown an appropriate test–retest reliability as well a substantial interrater agreement.[16]

ANI was defined by the following: (1) the presence of cognitive impairment demonstrated as a performance of 1 standard deviation (SD) or more below the mean of age- and education-adjusted normative scores in at least two domains, (2) the impairment does not interfere with everyday functioning, (3) the impairment does not occur solely as part of *delirium* or dementia, and (4) the diagnosis is only possible if the cognitive impairment cannot be explained by other comorbidities. MND was determined when (1) performance in at least two domains was 1 SD or more below the mean of age- and education-adjusted normative scores, (2) cognitive impairment produces at least mild interference in daily functioning: self-report or observation by a knowledgeable informant that the individual has undergone decline in at least ≥2 instrumental activities of daily living, (3) cognitive impairment does not meet criteria for *delirium* or dementia, and (4) it is not fully explained by comorbid conditions. To avoid overestimating the impact that frailty had on the dependent variable, all HIV-associated dementia cases were not considered in this study.[15]

Covariates

Sociodemographic variables included age, sex, and educational level (years of education). Participants were asked whether they had a documented diagnosis of diabetes, hypertension, dyslipidemia, cancer, myocardial ischemia, stroke, chronic obstructive pulmonary disease, cirrhosis, osteoarthritis, rheumatoid arthritis, osteoporosis, and/or chronic kidney disease. The presence of each of these diseases was summed up in a score ranging from 0 to 12 where a higher score indicates more comorbidities. The presence or absence of hepatitis C virus coinfection was registered. BMI [BMI = weight (kg)/height $(m)^2$] was calculated from direct measurements. Smoking status (current, former, or never) and alcohol intake (current, former, or never) were also investigated.

Current $CD4^+$ T lymphocyte counts were measured by means of flow cytometry (BD FACSCalibur™; BD Biosciences, San Jose, CA) and cell counts were treated as a dichotomous variable (≤200 vs. >200). $CD4^+$ cell count nadir values (the lowest count registered) were also considered for analysis. HIV-RNA levels (viral load [VL]) were measured using real-time polymerase chain reaction either on the Roche TaqMan® Analyzer 48 (Roche Molecular Diagnostics, Pleasanton, CA) or the Abbott m2000 RealTime System (Abbott Molecular, Inc., Des Plaines, IL) with a lower limit of detection of <40 copies/ml and treated as a dichotomous variable

(suppressed when <40 copies/ml and not suppressed when ≥40 copies/ml). All $CD4^+$ cell counts and VL determinations used for analysis were measured within 1 month of the clinical evaluation at the latest.

Time of HIV diagnosis, in years, was obtained from clinical records and calculated as the time elapsed from the documentation of HIV infection to the comprehensive geriatric assessment.

Time on HAART, in years, represents the time from the first HAART treatment administered until the date of clinical evaluation.

Statistical analyses

Variables were described using arithmetic mean and SD or frequency and proportion when appropriate. We used chi-square test to compare qualitative data, analysis of variance for continuous variables, and nonparametric tests when necessary.

To compare the different domains of cognitive function assessed by the NEUROPSI neuropsychological battery, *Z*-scores are reported. In addition, to determine an independent association between the phenotype of frailty and HAND, multinomial logistic regression models were constructed adjusting for potential confounders, including age, years of education, time of HIV diagnosis, VL, $CD4^+$ cell count, nadir $CD4^+$ cell count, and comorbidities. Risk ratio (RR) was chosen as the measure to express the strength of the associations. A *p*-value of .05 or less was considered significant, and the 95% confidence intervals (CI) are provided. All statistical analyses were performed using SPSS software for Windows® version 20.0 (SPSS, Inc., Chicago, IL).

Results

This study included 206 participants on HAART. Mean age was 60.5 years (SD = 6.3), 84.9% were male, and mean educational level was 12.8 years (SD = 5.1). Dyslipidemia (51.0%) and hypertension (28.6%) were the most frequent comorbidities. Regarding the frailty phenotype, 2.9% of patients were considered frail, 26.2% prefrail, and 70.9% nonfrail. The prevalence of HAND was 66.0% (ANI 60.2% and MND 5.8%).

Table 1 presents the comparative analysis of sociodemographic and health-related characteristics according to neurocognitive status. As expected, those with MND were older and had lower schooling; however, the differences were not statistically significant ($p = .396$ and $p = .059$, respectively). There were no statistically significant differences between HAND status and most of the variables considered in the present study, including $CD4^+$ cell count or VL. However, MND participants had significantly lower $CD4^+$ nadir cell counts compared with ANI and cognitively nonimpaired individuals. On the contrary, participants with ANI and MND showed significantly lower performances in all cognitive subdomains assessed by the NEUROPSI neuropsychological battery when compared with the cognitively normal (excluding the orientation domain). Nevertheless, the MND subgroup had particularly lower performances on executive functions ($p < .001$), visual memory ($p < .001$), and verbal memory ($p < .001$). Prefrail and frail statuses were more frequent among participants with MND when compared with either ANI or cognitively nonimpaired individuals ($p = .002$).

Multinomial logistic regression analyses of HAND are presented in Table 2. The unadjusted model shows that prefrail and frail statuses were associated with MND (RR = 6.31, 95% CI = 1.69–23.52; $p = .006$ and RR = 16.22, 95% CI = 3.30–79.71; $p < .001$, respectively) but not with ANI (RR = 0.85, 95% CI = 0.65–1.12; $p = .258$ and RR = 0.79, 95% CI = 0.35–1.78; $p = .576$, respectively). However, after adjusting for age, education, time of HIV diagnosis, VL, $CD4^+$ cell count, nadir $CD4^+$ cell count, and comorbidities, only the prefrail but not the frail subgroup remained significantly associated with MND (RR = 5.70, 95% CI = 1.09–29.82; $p = .039$ and RR = 18.31, 95% CI = 0.93–362.58; $p = .056$, respectively).

Discussion

The present study shows an association between the prefrail status and HAND, specifically MND, among PLWHIV aged 50 or older receiving care in Mexico City. This association is independent of age, years of HIV diagnosis, education, comorbidities, recent VL, nadir $CD4^+$ cell count, and recent $CD4^+$ cell count. Our results partially replicate the findings from previous studies performed in non-HIV-infected and HIV-infected individuals that show prefrail/frail status as a risk factor of cognitive impairment.[6,17–20] Given that data on frailty and neurocognitive disorders are limited in PLWHIV, our results add information relevant to the growing population of aged people living with HIV, particularly those outside the United States where the issue has not been appropriately addressed.

Interestingly, we found an unexpected low prevalence of physical frailty (2.9%) considering its frequency in previous studies of aging PLWHIV (5%–20%).[21–23] The relatively young mean age, improving retention, longer survival, and high HAART compliance resulting in viral suppression in our participants might explain this finding.[24,25] Nonetheless, we suspect that a strong survival bias may account for the low frequency of frailty since most PLWHIV older than 50 receiving care in Latin America were diagnosed and started receiving care at younger ages.[26] This low frequency may partially explain the lack of association between the frail subgroup and HAND after adjusting for potential confounders. Yet, the prefrail status, a condition that usually precedes frailty, was associated with mild cognitive impairment in this relatively young group of PLWHIV. While a threshold of 50 years of age may be considered too low to define an older person, the earlier development of non-AIDS-associated conditions,[5,27] higher levels of inflammatory markers, and accelerated immunosenescence,[28,29] among other factors, have led to an overall consensus that considers PLWHIV as older from an earlier age.[23] These factors have been also associated with frailty in PLWHIV.[30]

Frailty is a recognized risk factor for cognitive impairment among HIV-noninfected older adults.[31–33] In turn, HIV infection has been also associated with the early onset of frailty, particularly among those with a history of AIDS, even after achieving adequate viral suppression under HAART.[22] Moreover, it appears that PLWHIV have a higher frequency of cognitive impairment compared with those who are not infected. A recent cross-sectional study conducted in 345 HIV+ adults aged ≥40 years showed a higher prevalence of prefrailty/frailty status among persons neurocognitively impaired when compared with noninfected participants,[20] which

Table 1. Distribution of Demographic and Health-Related Characteristics According to HIV-Associated Neurocognitive Disorders Status in Older Adults (≥50 Years Old) Living with HIV

Variable	*Total,* n = *206*	*Normal,* n = *70* *(34.0%)*	*ANI,* n = *124* *(60.2%)*	*MND,* n = *12* *(5.8%)*	p*
Male, *n* (%)	177 (85.9)	64 (91.4)	104 (83.9)	9 (75.0)	.185
Age, mean ± SD	60.5 ± 6.3	61.2 ± 6.6	60.0 ± 5.7	61.1 ± 9.0	.396
Education (years), mean ± SD	12.7 ± 5.1	13.9 ± 5.0	12.3 ± 5.1	11.1 ± 5.5	.059
Number of comorbidities,[a] mean ± SD	1.4 ± 1.2	1.5 ± 1.4	1.3 ± 1.0	1.2 ± 1.0	.390
Diabetes, *n* (%)	34 (16.5)	13 (18.6)	19 (15.3)	2 (16.7)	.842
Hypertension, *n* (%)	59 (28.6)	23 (32.9)	32 (25.8)	4 (33.3)	.542
Dyslipidemia, *n* (%)	105 (51.0)	37 (52.9)	63 (50.8)	5 (41.7)	.772
Hepatitis C virus coinfection, *n* (%)	4 (3.1)	0 (0.0)	4 (5.1)	0 (0.0)	.266
Body mass index, mean ± SD	24.9 (3.9)	24.5 ± 3.9	25.2 ± 3.9	24.9 ± 3.9	.541
Current or former smoker, *n* (%)	33 (20.8)	14 (27.5)	18 (18.6)	1 (9.1)	.275
Current or former alcohol use, *n* (%)	36 (22.6)	15 (29.4)	20 (20.6)	1 (9.1)	.257
$CD4^+$ ≤200 cells/μl, *n* (%)	13 (6.3)	5 (7.1)	7 (5.6)	1 (8.3)	.879
Nadir $CD4^+$ cells/μl, mean ± SD	158.6 ± 132.6	169.8 ± 138.8	164.3 ± 130.3	59.5 ± 85.0	.047
Undetectable HIV RNA, *n* (%)	199 (96.6)	67 (95.7)	120 (96.8)	12 (100.0)	.740
Years infected with HIV, mean ± SD	11.1 (5.5)	11.1 (4.8)	11.1 (5.7)	11.5 (7.4)	.969
Z-scores for cognitive domains assessed by the NEUROPSI neuropsychological battery					
Orientation, mean ± SD	0.0 ± 1.0	−0.01 ± 0.90	−0.00 ± 1.10	0.13 ± 0.00	.850
Attention, mean ± SD	0.0 ± 1.0	0.24 ± 0.91	−0.12 ± 1.05	−0.33 ± 0.79	.014
Visual memory, mean ± SD	0.0 ± 1.0	0.26 ± 0.86	−0.10 ± 1.05	−0.65 ± 0.83	.002
Verbal memory, mean ± SD	0.0 ± 1.0	0.41 ± 0.88	−0.20 ± 0.98	−0.58 ± 1.17	<.001
Language, mean ± SD	0.0 ± 1.0	0.29 ± 0.73	−0.13 ± 1.12	−0.43 ± 0.67	.002
Visuospatial abilities, mean ± SD	0.0 ± 1.0	0.15 ± 0.96	−0.08 ± 1.01	−0.15 ± 1.11	.037
Executive functions					
Conceptual, mean ± SD	0.0 ± 1.0	0.31 ± 0.83	−0.17 ± 1.04	−0.23 ± 1.22	<.001
Motor, mean ± SD	0.0 ± 1.0	0.40 ± 0.67	−0.20 ± 1.06	−0.53 ± 1.33	<.001
Frailty status					.002
Nonfrail, *n* (%)	146 (70.9)	51 (72.9)	92 (74.2)	3 (25.0)	
Prefrail, *n* (%)	54 (26.2)	18 (25.7)	29 (23.4)	7 (58.3)	
Frail, *n* (%)	6 (2.9)	1 (1.4)	3 (2.4)	2 (16.7)	

[a]Number of the comorbidities is the number of self-reported comorbidities, which include diabetes, hypertension, dyslipidemia, cancer, myocardial ischemia, stroke, chronic obstructive pulmonary disease, cirrhosis, osteoarthritis, rheumatoid arthritis, osteoporosis, and chronic kidney disease (higher score means more chronic diseases).

*p-Value represents intergroup differences.

ANI, HIV-associated asymptomatic neurocognitive impairment; HIV, human immunodeficiency virus; MND, HIV-associated mild neurocognitive disorder; SD, standard deviation.

Table 2. Association Between Frailty and HIV-Associated Neurocognitive Disorders in Older Adults (≥50 Years Old) Living with HIV Using Logistic Regression Analysis

	ANI, 124 (60.2%)			*MND, 12 (5.8%)*		
	RR	*95% CI*	p	*RR*	*95% CI*	p
Unadjusted						
Nonfrail	1	—	—	1	—	—
Prefrail	0.85	0.65–1.12	.258	6.31	1.69–23.52	.006
Frail	0.79	0.35–1.78	.576	16.22	3.30–79.71	<.001
Adjusted[a]						
Nonfrail	1	—	—	1	—	—
Prefrail	0.92	0.69–1.23	.571	5.70	1.09–29.82	.039
Frail	0.85	0.36–2.00	.707	18.31	0.93–362.58	.056

[a]Age, years of education, HIV diagnosis time, viral load, $CD4^+$ cell count, nadir $CD4^+$, and comorbidities.

CI, confidence interval; RR, risk ratio.

is consistent with our findings. The frailty syndrome is a phenomenon not limited to one physiologic system, but instead represents the result of interactions and redundancy across multiple systems. Thus, frailty might be useful when describing the complexity of the interaction between the health problems that arise in aging PLWHIV, such as metabolic, cardiovascular, musculoskeletal, and immunological disturbances.[34] In this vein, Wallace *et al.* have shown that the frailty index (another holistic tool to identify highly vulnerable older adults) has an inverse association with the likelihood of ''successful cognitive aging,'' which should be considered as an important clinical outcome among PLWHIV.[35]

In PLWHIV, chronic inflammation resulting from the virus, cumulative drug toxicity, and high rates of social and behavioral risk factors have all been seen associated with frailty and may contribute to poor prognosis in this population.[36] It is very possible that both HIV infection and frailty share several pathophysiologic mechanisms, such as persistent inflammatory cell responses and chronic activation of lymphocytes. Considering this, it is plausible that the coexistence of HIV and frailty in the same individual will promote the early incidence of adverse health-related outcomes such

as cognitive decline. The spectrum of the frailty syndrome *per se* has been proposed as a generator of vascular changes (including the vessels of the central nervous system), which probably could explain the development of cognitive impairment among people living with or without HIV[37,38] Vascular damage has been persistently implicated in the genesis of different geriatric syndromes. The Cardiovascular Health Study demonstrated that the phenotype of physical frailty was associated with subclinical cardiovascular disease and with more infarct-like lesions in the brain.[39] Another recent report showed that subtle changes in nonconventional brain magnetic resonance imaging sequences that could preclude white matter hyperintensities are more frequently seen in frail older adults when compared with their nonfrail counterparts.[40] In our study, prefrailty appears to increase the likelihood of mild cognitive impairment among PLWHIV. Therefore, awareness of this association could lead to earlier identification of individuals at risk of developing dementia since epidemiological studies have shown that frailty is a risk factor for both vascular and neurodegenerative disorders.[6,41]

Even though there was no association between prefrailty/frailty and ANI, which represents the mildest form of the HAND spectrum, there was an association between the prefrail subgroup and MND but not between frail status and MND. These results suggest that early stages of frailty (as represented by the prefrail condition) in older PLWHIV may be associated with mild forms of cognitive decline, whereas frailty might be present among persons with a more severe cognitive impairment such as dementia. We cannot, however, test this hypothesis in this group since we did not include participants with dementia. The mechanisms for this association, however, remain unclear and a longitudinal approach is needed to clarify the role of prefrailty on HAND. In clinical practice, routine screening for frailty seems more feasible than a complete neuropsychological evaluation. Thus, frailty assessment could be used as a cue to perform a neuropsychological evaluation, ideally identifying individuals who would benefit from more comprehensive, time-consuming tests.

Unexpectedly, there was no significant association between VL or $CD4^+$ counts and cognitive impairment. This could imply that other mechanisms outside of immune-mediated responses could be involved in the cognitive decline observed in HIV-infected individuals. This lack of association can be explained by (1) the low heterogeneity of the study population since most of our patients had complete HIV viral suppression with $CD4^+$ counts well above 200 and (2) HAND persist in many persons despite a good immune recovery,[42] although with decreased severity.[43–45] Nonetheless, the depth of immune suppression reached by the participants, as represented by the $CD4^+$ nadir cell count, was associated with cognitive impairment, which could represent an important HIV ''legacy event'' that causes irreversible neural injury, thus contributing to HAND.[42] Our findings differ from the pre-HAART era, where the degree of immunosuppression was directly associated with neurocognitive impairment.[46–48]

The main limitation of our study is its cross-sectional design. While such design allowed us to identify an association, it precluded the determination of a causal link in either way of causation. Selection bias may have arisen due to the survival of healthier people, hence less prone to frailty. Also, the characteristics of predominantly male patients receiving care in a referral center could have contributed to selection bias. Therefore, our results must be interpreted with caution and require confirmation in different study populations. The strengths of our study rely on the use of validated tools to assess cognitive status and a comprehensive and standardized geriatric evaluation performed by experienced personnel. Furthermore, the number of participants enrolled in our study is noteworthy since it represents the largest population of PLWHIV where frailty and cognitive impairment have been assessed. In addition, this study provides evidence of the association between early stages of frailty and cognitive impairment, which has also been observed in middle-aged as well as older adults.[20]

In conclusion, prefrail status is associated with cognitive impairment in older adults living with HIV. An early stage of frailty is associated with an increased likelihood of presenting MND. Early frailty assessment in individuals living with HIV may be useful to identify simultaneous cognitive impairment and other geriatric syndromes. By doing so, an opportunity to implement early interventions to modify the course of frailty and potentially other consequences could become available. Whether improving frailty ultimately reduces the risk of cognitive impairment remains to be determined. Nonetheless, better understanding of the interplay between this geriatric syndrome and the risk of cognitive impairment in HIV older adults may, in time, translate in less disability and better quality of life for these patients.

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