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Research Article

Prevalence of Frailty Phenotype and its Association with the Immune Profile in Mexican People Living with HIV Aged ≥50

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Abstract

Background

The number of persons Living with HIV (PLHIV) older than 50 has increased significantly. Several similarities have been found between aging and HIV infection. Patients with HIV have premature complications usually observed in chronological age, usually called Geriatrics Syndromes (GS): e.g., depressive symptoms, disability, nutritional risk and Frailty Phenotype (FP). The immune profile has become relevant as a predictor of negative outcomes in the context of HIV infection.

Objectives

To determine the immune profile and its associations between FP in adults aged 50 or older, attending the HIV-AIDS clinics at a University-Affiliated Hospital in Mexico.

Methods

Cross-sectional study in participants aged ≥50, recruited between January 2015 and January 2017. Participants underwent a Comprehensive Geriatric Assessment (CGA), with which the diagnosis of FP and immune profile was obtained. Linear regression analyses were determined to establish the association between some baseline immune variables (CD4+ T cells/μL nadir, CD4+ T cells %, CD8+ T cells/μL and viral loud nadir) and frailty phenotype index.

Results

We included 116 subjects; mean age was 55 years (SD±6), women accounted for 20%. Overall, 14% were frailty. Linear regression analyses showed that immune baseline profile model (CD4+ T cells/μL nadir, CD4+ T cells %, CD8+ T cells/μL and viral loud nadir) did not reach statistically significance.

Conclusions

This study showed that the prevalence of FP is higher in Mexican PLHIV aged ≥50. Our combination of four baseline immune variables cannot explain the variation in the dependent variable (FP). These results suggest that the knowledge of the immune profile is not enough for a predictive use about frailty phenotype in Mexican PLHIV aged ≥50. We suggest that a global evaluation should be included in the promotion of health to prevent GS in the elderly community living with HIV.

Keywords: Frailty; Geriatric syndrome; HIV; Immune profile

Introduction

The number of aging People Living with HIV (PLHIV) has increased significantly since Highly Effective Antiretroviral Therapy (HAART) was available to the most of population. Thus, with the use of HAART infection has become a chronic disease [1]. In Mexico almost 20,000 cases have been recorded from 1983 to 2011 in people over 50 years of age (12.5% of the total population affected). In the US it is estimated that currently almost 50% of the HIV-infected population is over 50 years of age [2,3].

This change on HIV demography is so unexpected, that the American Society of Geriatrics and the American Academy of HIV had been to re-defined "elderly". In the context of people with HIV, all 50-year-olds and plus are considered as elders [4]. Several similarities have been found between aging and HIV infection: DNA damage and impairment of repair ability, neuroendocrine alterations, sarcopenia and immunological senescence phenomena. Patients with HIV have premature complications usually observed in chronological age: Cognitive impairment, falls, Frailty Phenotype (FP) and disability [5-12]. The FP has become relevant, as a predictor of negative outcomes in the context of HIV infection. Its presence at the start of antiretroviral therapy leads to an increase in morbidity and mortality, independently of age and any other factors [3,5,13]. Although there is currently no specific accepted definition of frailty in HIV-infected patients, it has been conceptualized as a health condition characterized by a decreased physiological reserve and poor response to stressors. One way to assess frailty is through the frailty phenotype proposed by Linda Fried [14]. The presence of the following is considered as frailty:

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Weight loss, weakness, low level of physical activity, self-report of exhaustion and decrease in gait speed [13-15].

It has been hypothesized that the premature aging of CD4+ T cells in HIV infection may play a fundamental role to the development of diseases observed in PLHIV aged ≥50. There is increasing evidence that chronic and harmful inflammation is present in PLHIV [16-21].

This study aims to determine the prevalence of Frailty Phenotype (FP) and its association between baseline Immune Profile (IP) among PLHIV aged ≥50, attending the HIV-AIDS clinics at a university-affiliated hospital in Mexico.

Material and Methods

Study population

Cross-sectional study including 116 participants aged ≥50, which were consecutively recruited from the HIV-AIDS clinics at a university-affiliated hospital in Guadalajara (a 1000-bed teaching hospital in the west of Mexico) between January 2015 and January 2017. Subjects were invited to voluntarily participate in the study the day of their scheduled medical visit. Once participants agreed, they underwent a Comprehensive Geriatric Assessment (CGA) by trained staff using standardized methods. Detailed socio demographic, immunological and GS information was also obtained. Subject who did not complete the questionnaire responses or did not authorize the inform consent were excluded to avoid the inclusion of incomplete covariates. The hospital ethic committee reviewed and approved the study protocol.

Assessments

Dependent variables: Frailty phenotype index was investigated as outcome.

Frailty Phenotype: To evaluate frailty phenotype, we used an index based on the original criteria published by Fried and Walston: Weight loss, self-report of exhaustion, pressure strength (according sex and body mass index), gait speed (according sex and height) and caloric expenditure by the Minnesota free time physical activity questionnaire [22]. For descriptive purposes FP has been presented as a categorical variable: participants were classified as non-frail when obtaining an overall sum of 0 points; they were considered pre-frail with a 1-point score, and frail with 3 or more points [14]. For the regression analysis it was presented as a continuous variable.

Immunological profile

Five immunological variables were investigated as independent variables: absolute CD4+ T cells/μL count nadir, CD4+ T cells percentage, absolute CD8+ T cells/μL count nadir, the CD4/CD8 ratio and viral load.

Viral load evaluation

HIV 1-RNA viral load in plasma was measured through the Roche Amplicor HIV-1 Monitor 1.5 Ultrasensitive PCR techniques. Controlled or undetectable HIV infection was considered if the viral load was ≤50 copies/mL, as a low viral load with a count between 51 to 199 cop/mL and in virologic failure if viral load was ≥200 cop/mL during at least six months under treatment.

Covariates

Socio-demographic variables included age, sex and morbidity variables. Body mass index was calculated as measured weight in kilograms divided by measured height in meters squared (kg/m^2). Individuals were considered as normal from 22.0 to 24; as overweighed 25 to 29; obese with >30, and malnutrition <22 [23]. A trained physician determined diseases according to standardized, well-known, pre-established criteria and algorithms combining information from self-reported diagnoses, medical records, current pharmacological treatment and clinical examinations. All participants were asked whether they had a diagnosis of any chronic diseases per the World Health Organization's International Classification of Diseases (ICD-10) [24].

Geriatrics Syndromes

Four conditions considered geriatrics syndromes were investigated as covariates: Disability, cognitive impairment, depression and malnutrition.

Disability

Impairment in basic (ADL) and Instrumental Activities of Daily Living (IADL) was used to identify disability measure by Lawton & Brody and Barthel indexes [25,26]. For each domain, if the participants indicated that they were unable to carry out at least one of the activities without assistance, they were considered as having disability.

Cognitive impairment

Cognitive function was assessed by the Mexican population validated version of the Mini-Mental State Examination (MMSE). The lower score was determined with a cut-off score of <23, adjusted by age and education [27].

Depression

Depressive symptoms were assessed using the validated version of the 15-item Geriatric Depression Scale (GDS). A cut-off point of >5 indicated the presence of depression [28,29].

Malnutrition

The nutritional risk was evaluated through the Mini Nutritional Assessment (MNA). The cut-off point of ≤23.5 indicated the presence of nutritional risk, and ≤17 was considered for malnutrition [30].

Statistical Analyses

Baseline descriptive data for the final sample are shown as means and standard deviations for continuous variables and frequencies for categorical variables. X^2 test or Fisher's exact test were used as appropriate. Linear regression analyses were used to determine the association strength for the frailty phenotype index and a elected set of immune profile variables. Univariate analyses were first performed to screen for predictor variables for Frailty Phenotype index. The choice of independent variables used in the univariate analyses was based on the review of literature and clinical judgment. In the next step, variables that were statistically significant at a P, 0.2 levels in the univariate analyses were included in multivariate regression model.

Estimated regression coefficients from the univariate and multivariate regression analyses were reported with 95% confidence intervals and P-values. The R^2 (coefficient of determination) and the Root Mean Square Error (RMSE) were reported as fit of regression model.

Regression diagnostics were performed to investigate any violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity (variance inflation factor and Durbin-Watson test).

All analyses were evaluated using 95% confidence intervals and a P-value of <0.05 was considered statistically significant. Statistical analyses were performed in Stata software for Windows® (Stata Corp., Texas, IL, version 14).

Results

The final sample was made up of 116 individuals aged ≥50; women accounted for 20%, and the mean of age was 55 (SD±6). The main baseline characteristics are presented in table 1 between those and the presence of non-frailty, pre-frailty and frailty phenotype.

	Not Frail	Pre-Frail	Frail
Variable (Total)	n (%)	n (%)	n (%)
Sex			
Female (20)	3 (15)	13 (65)	4 (20)
Male (83)	11 (13.3)	62 (74.7)	10 (12)
CDC clinical stage			
A1 (11)	2 (18.2)	8 (72.7)	1 (9.1)
A2 (6)	1 (16.7)	5 (83.3)	0
A3 (5)	0	5 (100)	0
B1 (8)	1 (12.5)	6 (75)	1 (12.5)
B2 (10)	3 (30)	5 (50)	2 (20)
C1 (18)	3 (16.7)	12 (66.7)	3 (16.7)
C2 (26)	1 (3.8)	21 (80.8)	4 (15.4)
C3 (19)	3 (15.8)	13 (68.4)	3 (15.8)
Related-HIV neurological disease			
Yes (17)	1 (5.9)	12 (70.6)	4 (23.5)
No (86)	13 (15.1)	63 (73.3)	10 (11.6)
HBV			
Yes (12)	0	11 (91.7)	1 (8.3)
No (91)	14 (15.3)	64 (70.3)	13 (14.3)
HCV			
Yes (8)	1 (12.5)	6 (75)	1 (12.5)
No (95)	13 (13.7)	69 (72.6)	13 (13.7)

Table 1: Prevalence of frailty phenotype according to the socio demographic and clinical characteristics.

Of the total, 34% of the sample was aged ≥50 years at the time of HIV diagnosis, and 64% had 50 years or more when initiated HAART. At baseline (after to start HAART), the 81% presented viral load undetectable (≤50 copies/mL), CD4+ T cells/µL count median was 418 (IQR: 270-619), CD8+ T cells/µL count median of 837 (IQR: 621-1164), a CD4/CD8 ratio media of 0.76 and just 7.8% had virologic failure. At time of HIV-diagnosis, 71% had <200 CD4+ T cells/µL, 66% had <14% of CD4+ T cells, the viral load median was 63650 copies/mL (IQR: 434-278323), CD4+ T cells/µL count nadir median was 99.9 (IQR: 41-205), with a CD4+ T cells percentage median of 9.1% (IQR: 5-15), and CD8+ T cells/µL count nadir with a median of 624 (IQR: 297-1086), and a CD4/CD8 ratio media of 0.27.

Nineteen percent presented a related-HIV neurological disease and 30% a cardiovascular disease. The prevalence of co-infection with hepatitis B virus was 11% and 9% for Hepatitis C virus.

A total of 8% had mild cognitive impairment and 27% had clinically significant depressive symptoms. The 3% of sample presented one or more disabilities in the IADL scale. As for the nutritional status, only 26% was on nutritional risk.

About FP index, 14% had three or more frailty phenotype components. Frailty components were as follows: 21% reported weight loss, 15.5% reported fatigue, 10.7% had lowered walking speed and 36% had insufficient grip strength.

The results from the univariate regression analyses of the associations between baseline variables and the frailty index score are presented in table 2. All independent variables with P, 0.2 are presented. Variables with lowers P-values were age at the time of HIV-diagnosis and age at initiation of HAART. The CD4/CD8 ratio was not significant at this level of analysis.

Predictor Variables, Per SD	Simple Regression	Multiple Regression
	β (SE), P-value	β (SE), P-value
Age	0.276 (0.011), 0.003	
Sex	-0.039 (0.221), 0.676	
Co-morbid	0.143 (0.074), 0.124	
Age at the time of HIV-diagnosis	0.206 (0.009), 0.027	
Age at initiation of HAART	0.227 (0.009), 0.014	
Years living with HIV-diagnosis	-0.087 (0.013), 0.355	
Years living with HAART	-0.100 (0.015), 0.285	
CD4 nadir	-0.036 (0.001), 0.698	0.083 (0.001), 0.575
CD4 %	-0.088 (0.010), 0.356	-0.150 (0.016), 0.304
CD8	-0.009 (0.000), 0.923	-0.032 (0.000), 0.751
Viral loud nadir	0.047 (0.000), 0.617	0.049 (0.000), 0.605
CD4 nadir	-0.036 (0.001), 0.698	0.083 (0.001), 0.575

Table 2: Coefficients (95% CI) for the effects of a standard deviation increase in frailty index scores at baseline on change in predictor variables scores.

The baseline for 4 immunological HIV-related variables was the model of the multivariate regression analysis. This included CD4+ T cells/µL nadir, CD4+ T cells %, CD8+ T cells/µL and viral loud nadir. Lower nadir score for CD4+ T cells/µL and CD4+ T cells percentage were associated with worst FP scores (b= -0.036, b= -0.088). However, the model did not reach statistically significance.

Discussion

The results demonstrate that lower baseline in immune profile in PLHIV aged ≥50 in a Mexican population were no statistically significant predictor of worst frailty score. Thus, our study showed no association between some baseline immune variables and the frailty phenotype index in PLHIV aged ≥50 in a Mexican population.

However, a strong association has been observed repeatedly between HIV infection and FP. The findings most pronounced have been

demonstrated among men with low CD4+ T lymphocyte count (<350 cells/μL), high viral load (>100,000 copies/mL), clinically defined AIDS, longer duration of HIV infection and older age [21]. Association between frailty and low CD4+ T lymphocyte count has been replicated in other cohorts. In the Women's Interagency HIV Study (WIHS), frailty was higher among HIV-infected women with AIDS (12%) or with a CD4+ T lymphocyte count <100 cells/μL (20%) compared to HIV-uninfected women (8%), HIV-infected women without AIDS (7%), or HIV-infected women with CD4 count >500 cells/μL (6%) [31].

We believe that variations in the cut-off to measure immunologic profile among all studies may explain the absence of statistical significance of our results between low CD4+ T lymphocyte count, viral load, and FP index.

By other hand, in the HAART era, men with a high viral load (>50,000 copies/mL) did not manifest frailty more frequently than those with low viral load (<400 copies/mL) after adjustment for age [32-34]. These results are comparable with our findings; in which neither the viral load level nor baseline CD4 cells/μL lower scores explained the worst FP scores.

Thus, to the best of our knowledge, this is one of the first studies to identify PLHIV aged ≥50 with the FP through the Fried index in Latin America. Studies have reported a prevalence of frailty between 5-33% in routine PLHIV care [32-39]. In our study we found a prevalence of FP of 14%. Variations in the frailty definition limit the comparisons of frailty prevalence between study populations. This study also it is the first in which the FP subtypes have been described in PLHIV so we don't know if they are similar from other regional studies.

In summary, these results showed that the presence of worse scores in certains immune baseline variables had no association with low scores in the Fried index for FP in PLHIV aged ≥50.

Now it is clear that PLHIV suffer from an accelerated aging due to the persistent and chronic activation of the immune system that leads to immune exhaustion and accelerated immunosenescence, even when on optimal immuno-virological control treatment [40]. Several associations between frailty and HIV infection have been suggests in previous research [41,42]. From a molecular perspective, both may share similar changes that could lead to a series of inter-related multi-systemic implications [43]. A clinical expression of this phenomenon is an increased prevalence of aging-related non-HIV associated comorbidities. Thus, HIV-infected patients are biologically older than their chronological age, and they suffer from aging-related problems, such as FP [40].

In a sample with characteristics similar to ours, Ávila-Funes et al., found that in the city of Mexico, the mean age in PLHIV was 59 years, and the majority were men (83%): a gender distribution identical to that of our work. In the same way, all the participants were receiving HAART at the time of the study. One of the main differences is our disability rate. While they found disability in IADL of almost 18%, our participants had only 3%. It is likely that this can be explained by the better immunological status and the youth of our sample compared to that of Mexico City [41].

Our study has several limitations. First, it is a cross-sectional design and is not possible to know the direction of the associations found. Second, this is a non-probabilistic sample; participants were recruited consecutively to participate in the study, per the attendance at their medical consultation, in a clinical for HIV-patients. The sample was probably consisted of individuals with highly heterogeneous characteristics, as higher self-care levels; so the participants had better baseline immune profile.

However, the main strengths of this study include GS screening, which was done with standardized tests. The population evaluated in our study is one of the most numerous in comparison to others reported in previous studies. Our preliminary results require future confirmation studies with a larger sample size and a longitudinal design.

Conclusion

This study showed that the prevalence of FP is higher in PLHIV aged ≥50 in Mexico (14%). Our combination of immune variables cannot explain the variation in the dependent variable (FP index). The presence of FP and its potential negative effects are some of the challenges of this time in which HIV infection has become a chronic disease with which it is possible to grow old. These results suggest the importance of monitoring other covariates, like GS, as they seem to have an impact on health status of the elderly population with HIV.

We think that Comprehensive Geriatric Assessment it is a tool to promote positive changes at the individual level and have the potential to establish therapeutic strategies in multiple levels to avoid the development of FP in the elderly community living with HIV. We believe that lowers scores of certain geriatrics syndromes could have a stronger and independent association with frailty phenotype than other factors, including immune profile. However, these results must be replicated in a more extensive cohort with a longitudinal approach.

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