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Comparison of Cerebrovascular Risk between Elderly Human Immunodeficiency Virus-seropositive Patients Treated with Highly Active Antiretroviral Therapy and Human Immunodeficiency Virus-seronegative Patients

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Abstract

Introduction: The current era of AIDS is characterized by an aging of population and increase in the incidence of non-acquired immune deficiency syndrome-related diseases. The aim of the present study was to compare the cerebrovascular risk in elderly HIV(+) patients under HAART therapy with seronegative elderly.

Materials and method: This transversal study was performed between January 2011 and December 2013, and evaluated 2 groups of individuals older than 60 years. The first group included elderly HIV(+) patients who had been receiving HAART for over 1 year, and the second group included elderly HIV(−) patients. To detect cerebrovascular risk in groups, anthropometric assessments (body mass index and waist circumference), clinical evaluations (Framingham score), and laboratory assessments (carotid Doppler ultrasonography and brain magnetic resonance imaging [MRI]) were performed.

Results: The HIV(+) group included 26 patients and the HIV(−) group included 40 patients. The cerebrovascular risks based on body mass index (P=0.001), the Framingham score (P=0.02), and the presence of lesions on MRI (P=0.03) were lower in the HIV(+) group than in the HIV(−) group. Moderate to severe cerebrovascular risk according to the Framingham score was 3 times more likely among infected patients than among non-infected patients (P=0.03). Additionally, patients who had received more than 10 years of HAART had a 90% lower chance of cerebrovascular disease if they presented with a Framingham score indicating moderate to high risk than if they presented with a Framingham score indicating mild risk (P=0.03).

Conclusion: Our results suggest that the presence of HIV infection in elderly patients might increase the risk of cerebrovascular events. The risk might be low in patients who receive HAART for more than 10 years, indicating that HAART might have the potential to reduce the risk of cerebrovascular events.

Keywords: AIDS; Cerebrovascular risk; Elderly; HAART

Introduction

Since the emergence of a potent combination therapy of antiretroviral agents in 1995 (highly active antiretroviral therapy [HAART]), patients who correctly follow the treatment regimen typically experience significant immunological improvement and viral suppression [1]. Mortality rates have dramatically improved, and the human immunodeficiency virus seropositive (HIV(+)) population is beginning to age [2]. In Brazil, the number of new diagnoses of HIV is increasing among patients aged 50–59 years and those aged ≥ 60 years, which, in addition to the survival of infected patients, has contributed to the increasing prevalence of HIV infection in the elderly [3].

In young patients, the risks of cardiovascular and metabolic complications associated with HAART have been well described [1-3]. Elderly HIV(+) patients have also been reported to experience unwanted side effects after HAART, as the risk of cardiovascular diseases, such as myocardial infarction and stroke, significantly increases with both age and exposure to therapy [4]. These events are referred to as non-acquired immune deficiency syndrome (AIDS)-related complications, and they include diseases such as cerebrovascular diseases, cancers, dementia, osteoporosis, and general fragility. These diseases develop because of a complex set of factors that are influenced by the infection itself, antiretroviral therapy, and patient behavior. In many cases, these factors lead to a peculiar clinical course in patients with HIV infection when compared to the course in patients not infected with HIV [5].

Considering these facts, we questioned whether the long-term metabolic effects of HAART, the inflammatory process of infection, and senescence might all contribute to a higher risk of cerebrovascular disease in elderly HIV(+) patients than in elderly HIV seronegative (HIV[−]) patients. Thus, the aim of the present study was to compare the cerebrovascular risk in elderly HIV(+) patients under HAART therapy with that in elderly HIV(−) patients.

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Materials and Method

This was a cross-sectional cohort study that included elderly outpatients (aged ≥ 60 years) at the Federal University of Triângulo Mineiro (UFTM), Uberaba, Minas Gerais State, Brazil between January 2011 and December 2013. The study was approved by the ethics committee of the UFTM in 2009 (protocol number 1541). The study required a minimum of 48 HIV(+) patients and 96 HIV(−) patients. Patients were invited to participate and we recruited for regular consultation.

The patients were divided into a HIV(+) group and a HIV(−) group. The HIV(+) group included HIV(+) patients who had been receiving HAART for at least 1 year, with frequent consultations and treatment at the Clinic of Infectious and Parasitic Diseases of the UFTM. The HIV(−) group included HIV(−) patients who were regularly monitored at the Geriatric Outpatient Department of the UFTM. In both groups, the patients had at least 1 chronic disease. The control group included patients with the same co-morbidity profile, except hypertension and cardiovascular events. The most common co-morbidities were hypertension, osteoarthritis, depression, osteoporosis, dyslipidemia, diabetes, and hypothyroidism. The demographic variables assessed were age, sex, occupation, smoking, education, and level of physical activity. In the HIV(+) group, we also collected data on the time of HIV infection, duration of regular HAART, current levels of CD4+ T lymphocytes, viral load, and use of protease inhibitors.

Cerebrovascular risk was evaluated using anthropometric measurements, the Framingham score (risk for cerebrovascular disease in 10 years), carotid Doppler ultrasound, and magnetic resonance imaging (MRI) of the skull. Risk factors for stroke in the Framingham score were age, hypertension, use of antihypertensive drugs, diabetes mellitus, smoking, presence of previous cardiovascular disease (myocardial infarction, angina, or peripheral atherosclerotic disease), congestive heart failure, atrial fibrillation, and left ventricular overload on electrocardiography [6,7]. The score was used to determine the risk of cerebrovascular events (mild [<10%], moderate [10–20%], or high [>20%]), as previously described [6,7]. Doppler ultrasonography of the carotid arteries is a simple, inexpensive, and minimally invasive technique for detecting subclinical atherosclerotic disease, and can be used to accurately predict the risk of cerebrovascular and cardiovascular events [8]. Examinations were performed in the Department of Radiology and Diagnostic Imaging at the UFTM, by an examiner who was blinded to the study objectives and the serological status of each patient. The device used was GE Logic 3 Expert (GE Healthcare, Milwaukee, WI), with a linear transducer having frequencies between 4 and 10 MHz, which is recommended for this examination [9,10]. Diagnostic findings were described according to the presence and morphology of plaques, flow velocities, and hemodynamic consequences, based on the criteria developed by Strandness and the Moneta index [11].

The correlation between the presence of cerebral white matter lesions (detected on MRI) and cerebrovascular disease has already been described, and it can be used to predict latent cerebrovascular disease [12]. We used a Magnetom Avanto 1.5 Tesla Class I MRI system (Siemens Medical Solutions, Erlangen, Germany), with multiplanar T1-weighted, T2-weighted, fluid attenuation inversion recovery, and diffusion sequences without contrast infusion. The images were evaluated by 2 physicians who were blinded to the objectives of the study and the serological status of each patient. Findings were classified according to the presence of hyperintensities on T2 sequences, using an ascending scale of severity and frequency (Fazekas classification) [10]. The scale was as follows: 0, absent; 1, rare foci of hyperintensities; 2, tenuous halos; 3, irregular halos extending deep into the white matter.

Anthropometric data related to cardiovascular risk and nutrition, including weight, body mass index (BMI), and waist circumference (WC), were assessed. Weight and height were measured using a digital scale, according to established guidelines for calculating BMI [13]. The digital weight scale had a maximum capacity of 150 kg and 100 g divisions. The reference values for BMI were adjusted for age [13]. WC was measured by a single examiner using a flexible and inelastic tape measure (3M, Maplewood, MN; 150 cm in length). The WC values were obtained at the lesser curvature located between the ribs and the iliac crest, without compressing the tissues. The cut-off points for WC were 80 cm in women and 94 cm in men, according to the findings for high risk of cardiovascular disease in a previous study [14].

The data were stored in a database created using Microsoft Office Excel 2010 (Microsoft Corporation, Redmond, WA), and the data were subsequently exported to SPSS version 17.0 (IBM Corporation, Armonk, NY) for analysis. The variables were reported using descriptive statistics (mean, standard deviation, standard error, median values, minimum and maximum, and percentiles). Data were analyzed for normality (Kolmogorov–Smirnov and Bartlett tests), homogeneity (Levene test), intergroup differences (Student's *t*-test and Wilcoxon and/or Mann-Whitney tests), and correlation (Pearson linear correlation coefficient for parametric variables and Spearman correlation coefficient for nonparametric variables). To estimate the magnitude of the associations among variables, the time of HAART use, and the presence of infection, odds ratios (ORs) were calculated with 95% confidence intervals (CIs) using univariate logistic regression. A P-value <0.05 was considered statistically significant.

Results

The study initially included 115 patients, with 46 patients in the HIV(+) group and 69 patients in the HIV(−) group. However, 37 patients were excluded because of incomplete evaluations and 12 patients were lost to follow-up. Therefore, 66 patients were finally included in the present study, with 26 patients in the HIV(+) group and 40 patients in the HIV(−) group. Of the 26 patients in the HIV(+) group, only 20 underwent MRI. Nevertheless, all patients were included in our analyses. The mean age of all patients was 67.73 ± 5.55 years (range 60–81 years). In the HIV(+) group, HIV infection was diagnosed at a mean of 9.54 ± 5.95 years before enrollment and HAART was being taken for a mean of 8.78 ± 5.74 years. The minimum interval between diagnosis and HAART was 1 year, and the maximum interval was 20 years. With regard to clinical status, in the HIV(+) group, 17 patients (65%) showed good control with undetectable viral load (<50 copies/mm^3) and 20 patients (77%) responded well to treatment (lymphocyte count >500 cells/mm^3).

The statistical data for each study variable in each group are summarized in Table 1, and the parameters of the Framingham score regarding the presence of HIV infection in both groups are presented in Table 2. BMI and WC were lower in the HIV(+) group than in the HIV(−) group. There was a significant difference in the duration of HAART relative to the scale of Fazekas cerebrovascular lesions between the groups (P=0.03). The cerebrovascular risks based on BMI (P=0.001), the Framingham score (P=0.02), and the presence of lesions on MRI (P=0.03) were lower in the HIV(+) group than in the HIV(−) group. Moderate to severe cerebrovascular risk according to the Framingham score was 3 times more likely among infected patients than among non-infected patients (P=0.03). Additionally, patients who had received more than 10 years of HAART had a 90% lower

Variables	HIV+ n=26	HIV− n=40	P-value
Age Average (SD)	65.8 (4.78)	68.7 (5.53)	**0.01***
Sex: Male (%) Female (%)	12 (46) 14 (54)	19 (47.5) 21 (52.5)	**0.43**
Body Mass Index Average (SD)	23.05 (3.16)	26.15 (4.21)	**0.001***
Waist Circumference (cm) Average (SD)	95.44 (7.39)	97.70 (8.16)	**0.32**
Framingham Score Average (SD)	8,10% (4.59)	14% (10.40)	**0.02***
Fazekas Score n (%) (Fazekas I to III)	17 (85)	40 (100)	**0.03***
Carotid US n (%) (Presence of Plaques)	15 (57.7)	25 (62.5)	**0.43**

*Statistically Significant; HIV: Human Immunodeficiency Virus; US: Ultrasonography

Table 1: Group averages for demographic data and status of infection.

Variables	OR[a]		95% CI[b]	χ^2 [c]	P[d]
	HIV-	HIV+			
Dyslipidemia	1.00	1.17	0.54–2.52	0.04	0.839
Glycemia	1.00	0.73	0.34–1.60	1.46	0.228
Hypertension Presence	1.00	0.26	0.07–0.92	2.07	0.03*
Cardiovascular event in 6 years	1.00	5.77	1.18–28.24*	2.16	0.03*
Presence of Atrial Fibrillation	1.00	0.28	0.12–2.14	1.78	0.84
Tabagism	1.00	1.32	0.89–3.24	2.31	0.69
Left Ventricular Hypertrophy	1.00	0.66	0.31–1.16	0.86	0.35

HIV, human immunodeficiency virus
a=Odds ratio; b=95% confidence interval; c=chi-square; d=P-value; * P < 0.05

Table 2: Evaluation of changes in conditions which compound the Framingham score in relation to the presence or absence of infection.

chance of cerebrovascular disease if they presented with a Framingham score indicating moderate to high risk than if they presented with a Framingham score indicating mild risk (Table 3).

Discussion

In the post-HAART era, AIDS has acquired the characteristics of a chronic disease. The CASCADE study found that the average life expectancy with infection was 6.3 years, which is slightly lower than that in our population (9,5 years) [15]. However, this is expected considering that in countries with a high prevalence, patients have a very high mortality profile [14,15]. In our HIV(+) group, most patients could be considered to have chronic infection, as they have been infected with HIV and have survived with HAART for over 5 years, which is a sufficient period to observe the impact of HAART on the effects of aging.

We noted good clinical control of HIV infection, as most patients had a viral load of <50 copies/mm^3 in blood and a lymphocyte count (CD4+) of >500 cells/mm^3. These findings suggest good patient adherence to the treatment protocol, which is consistent with the results of a previous study that found an adherence rate of 80% for ART among elderly outpatients [16].

On assessing cardiovascular risk based on anthropometric parameters, we found that BMI and WC were lower in the HIV(+) group than in the HIV(−) group, which may indicate low central obesity in HIV(+) patients. Studies that evaluated anthropometric parameters have shown a higher risk of obesity in HIV(+) patients than in the general population [17,18]. Amorosa et al. demonstrated that there is a high likelihood of metabolic syndrome and obesity in HIV(+) patients in the post-HAART era, unlike the high prevalence of consumptive syndrome prior to the introduction of HAART [19]. The prevalence of metabolic syndrome in these patients has been reported to be 14–18%, depending on the diagnostic criteria applied [18-20].

On analyzing the clinical cardiovascular risk profiles in our patients, we found that Framingham scores indicated a lower risk in the HIV(+) group than in the HIV(−) group, and moderate to severe cerebrovascular risk according to the Framingham score was 3 times more likely among infected patients than among non-infected patients. Besides the presence of infection, our analysis found that the time of HAART use was an influential factor for low-risk cerebrovascular disease (according to the Framingham score) and for a low incidence of prior cerebrovascular disease, especially in patients who had received HAART for more than 10 years. These results agree with those of a previous report that demonstrated the benefits of good control of infection in reducing cerebrovascular risk [21].

Previous prevalence studies that prospectively assessed cardiovascular outcomes have demonstrated the protective effects of HAART on cardiovascular disease [22,23]. Another study that evaluated HAART adherence in young patients concluded that discontinuation of treatment increased the risk of cardiovascular and cerebrovascular events [24]. Additionally, data from a randomized, prospective observational study have revealed a reduction in the incidence of cardiovascular disease with HAART, especially when the type of medication, viral load, and number of CD4+ T lymphocytes were taken into account [25]. One possible explanation for the reduction in the incidence of cardiovascular disease is that the immunological improvement associated with treatment reduces systemic inflammation, leading to a reduction in the risk of vascular events [23-25].

In addition to the traditional risk factors evaluated by the Framingham score, many studies have suggested that there are other risk factors associated with HIV infection because it involves potentially severe inflammatory activity indicated by impaired fibrinolysis and elevation of inflammatory mediators [24,25]. Therefore, the Framingham score alone might not accurately reflect the potential risk

Variables	OR			χ^2	p
	1 to 5 years (95% CI)	6 to 10 years (95% CI)	>10 years (95% CI)		
Framingham Mild vs Moderate to High	0.35 (0.09–1.35)	1.04 (0.16–6.97)	0.09 (0.01–0.76)*	8.88	0.03*
Presence of carotid plaques	0.84 (0.23–3.13)	2.40 (0.24–23.53)	0.48 (0.11–2.07)	1.91	0.59
Fazekas 0 vs. I to III	0.66 (0.04–10.25)	4.71 (014–151.4)	2.89 (0.11–71.93)	9.76	0.51

*Statistically Significant; CI: Confidence Interval; OR: Odds Ratio; HAART: Highly Active Antiretroviral Therapy

Table 3: Assessment of the risk of anatomical and biochemical complications with respect to length of HAART treatment.

of cerebrovascular disease in these patients. The association between systemic infections and malignancies should not be neglected, as it can increase the risk of the development of a hypercoagulable state [26].

Although studies have compared HIV(+) patients with HIV(−) patients, it remains inconclusive whether the influence of cerebrovascular risk factors is more marked in the presence of infection. Some studies [26] that examined subclinical cardiovascular disease in HIV(+) patients have suggested that the risk factors are greater in these patients than in HIV(−) patients at a young age, and therefore, HIV(+) patients should be screened at an early age. However, it is not clear whether this was a consequence of infection, HAART, or senescence itself [26].

In the present study, we also characterized cerebrovascular risk using carotid ultrasonography to detect atherosclerotic plaques and their hemodynamic effects. Several previous studies [26] have used this method to identify subclinical atherosclerosis in HIV(+) patients receiving HAART and thereby predict the risk of future cerebrovascular disease. However, these studies have shown mixed results, as the therapeutic effect of HAART may have masked any associated risk increase. We found a high prevalence of atherosclerotic plaques in both groups, with less intensity in the HIV(+) group than in the HIV(−) group; however, the difference was not significant. Similar studies have compared patients with and those without the use of protease inhibitors during HAART [27], and these studies did not detect significant intergroup differences, which is similar to our findings.

In addition to ultrasonography, the presence and magnitude of cerebrovascular diseases can be evaluated using MRI. These diseases include stroke and dementia, which are feared by patients considering their impact on quality of life and mortality. The presence of dementia associated with HIV has reduced dramatically since the introduction of HAART. Nevertheless, various degrees of cognitive impairment have been detected in patients with controlled viral load. Some studies have mentioned that chronic infection may trigger other mechanisms, exposing patients to the early onset of other common forms of dementia, such as vascular dementia and Alzheimer's disease [28,29]. In a recent American review of the incidence of stroke, a retrospective analysis showed a 60% higher risk in HIV(+) patients than in HIV(−) patients [29]. As HIV infection can cause stroke through several mechanisms, as described above, further studies should be conducted to elucidate the mechanisms, using seronegative patients, as well as patients who are and those who are not receiving HAART. While the majority of our patients had some degree of cerebrovascular disease, there was no significant difference between the groups, and therefore, cerebrovascular disease is likely related to senescence.

Interestingly, neuroimaging studies [28] that evaluated HIV(+) patients tended to include young patients, with mean ages ranging from 40 to 45 years. Cerebrovascular disease was previously a rare complication in HIV-infected patients; however, it has become a common occurrence with the increase in survival associated with HAART and the metabolic effects of the drugs [29]. A previous study attempted to retrospectively correlate the finding of cerebrovascular disease with cognitive impairment in patients aged >50 years, regardless of vascular outcomes and without including seronegative patients [29]. In contrast, we examined various vascular outcomes and included seronegative patients as controls.

The "Hawaii Aging with HIV Cohort Study" examined 62 elderly HIV(+) patients to detect white matter lesions and found that approximately half of the patients had moderate cerebrovascular disease and cortical atrophy, as detected on MRI [30,31]. These results are similar to those of our study, which found that 65% of patients had cerebrovascular disease according to the Fazekas classification.

The present study had several limitations. The study included a small number of HIV(+) patients, and HIV(+) patients not receiving HAART were absent owing to ethical considerations as current guidelines recommend the early introduction of HAART. A previous epidemiological study suggested that elderly patients were usually diagnosed in advanced stages of the disease and that they required immediate use of medications [15]. The selection of our control group may have been biased, as we recruited patients from a tertiary healthcare center and the risk of cardiovascular disease may have been higher in these patients than in the general population [32,33]. In future studies, patients should be recruited from primary healthcare facilities to help avoid bias, as these patients typically have a low risk of cardiovascular disease.

In conclusion, our results suggest that the presence of HIV infection in elderly patients might increase the risk of cerebrovascular events. The risk of cerebrovascular events might be low in patients who receive HAART for more than 10 years, indicating that HAART might have the potential to reduce the risk of cerebrovascular events. However, we were unable to establish causality between HAART and cerebrovascular risk, and additional studies are needed. Elderly AIDS patients with good clinical control might have a risk profile that resembles that of similar uninfected elderly patients.

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