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Pursuing Dementia in People Living with HIV: Prevalence and Associated Factors

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Abstract

Introduction: *The human immunodeficiency virus (HIV) is the leading cause of neurocognitive impairment in people over 40. The development of highly active antiretroviral therapy (HAART), the comprehension of disease pathogenesis, and the constant search for better life quality in people living with HIV have led to the HIV disease chronic evolution. Hence, it has been common to observe chronic diseases such as HIV-associated neurocognitive disorder (HAND). Unfortunately, the practitioner's unfamiliarity with HAND screening and treatment has contributed to poor patient care.*

Methods: *We evaluated 134 patients living with HIV and performed two tracking tests, the Mini-mental, which evaluates cortical dementia, and the International HIV Dementia Scale, which evaluates subcortical dementia.*

Results: *We observed dementia associated with HIV (HAD) in 29 patients (prevalence of 21.6%; CI 95%: 15.0 – 29.6). The independent factors related to HAD in this study, with statistical significance, were age (RPaj 1.05; CI 1.00 – 1.09; p=0.033), TCD4+ nadir (RPaj 0.998; CI 95% 0.996 – 0.999; p=0.03), and more than two years of detectable HIV viral load (RPaj 2.35; CI 95% 1.27 – 4.33; p=0.006).*

Discussion: *The prevalence of dementia related to HIV in our study was similar to the Brazilian and International data. Early diagnosis and treatment are fundamental for preventing HAND development, especially in older patients.*

Introduction

The human immunodeficiency virus (HIV) is responsible for the 20 and 21 century's biggest pandemic and, as it continues to expand, affects patients 50 years old and older (de Almeida et al., 2006; Palella et al., 1998; Saylor et al., 2016). The exact central nervous system (CNS) viral infection mechanism is unknown, but researchers believe in multiple pathways (de Almeida et al., 2006; Zayyad & Spudich, 2015). The neurological involvement in HIV infection occurs at the early stage, immediately after the HIV systemic infection, and its topography is subcortical, leading to neurocognitive disorder (de Almeida et al., 2006; Valcour et al., 2012; Zayyad & Spudich, 2015).

One of the probable pathways is that HIV enters the CNS via infected monocytes and macrophages, which are infected through CD4 receptors and CCR5 and CXCR3 co-receptors. These infected cells cross the blood-brain barrier (BBB) and enter the CNS (de Almeida et al., 2006). Another possibility is that viral particles, such as the Tat viral protein, cross the BBB (weakened due to the systemic inflammation caused by HIV) and trigger local inflammation (de Almeida et al., 2006; Zayyad & Spudich, 2015).

The CNS is chronically infected and damaged once not all HAART penetrates the CNS (Letendre et al., 2008). Hence, the antiretrovirals were classified according to CNS penetration which is influenced by their size, weight, pharmacokinetics, and pharmacodynamics. Thus, the CNS-penetration effectiveness score (CPE score) was elaborated. The HAART are classified as poor CNS penetration (score 1) to high CNS penetration (score 4) (Letendre et al., 2008). A CPE above or equal to 8 (the sum of all HAARt the patient takes) is recommended for possible CNS protection (Ministerio da Saude, 2013).

The HIV-associated neurocognitive disorder (HAND) is an expression to describe the HIV neurological disorder, which can be clinically classified as asymptomatic/mild (AND), moderate (MND), or severe/dementia (HAD). HAD is characterized by the presence or absence of conscience, significant loss of cognition, and daily activities. Furthermore, patients must score below two standard deviations on neuropsychological tests (Antinori et al., 2007; Shapshak

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et al., 2011).

Researchers have studied several ways of controlling and preventing HAND, but it is still prevalent worldwide (15 – 55%) (Saylor et al., 2016).

There is no pathognomonic clinical exam or image to diagnose HAND. Hence, practitioners must perform tracking tests such as the International HIV Dementia Scale (IHDS) and neuropsychological tests and exclude other organic diseases (de Almeida et al., 2006; Saylor et al., 2016; Stingele et al., 2001; Zayyad & Spudich, 2015). This study aims to track HIV-associated dementia (HAD) using the IHDS in people living with HIV (PLHIV) to understand HAD's prevalence and risk factors in our outpatient clinic and improve patient care.

Materials and Methods

This cross-sectional, observational, non-probabilistic sampling study involved patients from the Universidade Federal de Sao Paulo (UNIFESP) Infectious Disease Outpatient Clinic from 2011 to 2013. They were selected by simple random sampling once all population records were available. The UNIFESP Ethics Committee approved this study (number 125.861), and all patients received a consent form before enrollment. All subjects were interviewed by the same researcher and applied the Mini-Mental and IHDS to track HIV-associated dementia (HAD). We used the IHDS cutoff of 10 because it is the official cutoff used as a risk factor for dementia.

The inclusion criteria were patients diagnosed with HIV serotype 1, between 18 – 60 years of age, clinically stable, and without AIDS. The exclusion criteria were patients with hepatitis B and/or C coinfection, alcohol or other drugs dependence, any past or current medical history of CNS opportunistic disease, any past or present medical history of CNS vascular disease, any previous or current mental health disorder, in use of any medication with CNS penetration, any previous or current CNS neoplasm, uncontrolled metabolic disease, and hypothyroidism or hyperthyroidism.

We analyzed the variables sex, age, education, time length of HIV infection, TCD4+ nadir, TCD4+ at the recruitment, first HIV viral load documented, HIV viral load at the recruitment, time length of highly active antiretroviral therapy (HAART), continuous use of HAART, types of HAART used, antiretroviral CNS-penetration effectiveness score (CPE score), time length of TCD4+ < 500 cells/mm3, time length of TCD4+ < 200cells/mm3, time length of detectable HIV viral load, body mass index (BMI), controlled comorbidities such as hypertension (HT) or diabetes mellitus (DM), IHDS score, and Mini-mental score.

To determine the independent variables associated

Variables	nº	%
Sex		
Male	72	53.7
Female	62	46.3
Age (years)		
Mean (dp)	42,7 (8,3)	
Median (min - max)	44 (23 - 60)	
≤ 45	85	63.4
> 45	49	36.6
Education (years)		
Analphabet	3	2.2
1 a 5	23	17.2
6 a 9	33	24.6
10 a 12	37	27.6
> 12	38	28.4
BMI (kg/m^2)		
Mean (dp)	24,8 (3,8)	
Median (min - max)	24,5 (16 - 41)	
Sexual Orientation		
Heterosexual	105	78.4
Homosexual	18	13.4
Bisexual	10	7.5
Blood Transfusion *	1	0.7
*The Only case of HIV transmission besides sexual route		
Number of comorbidities (HT / DM)		
0	108	80.6
1	24	17.9
2	2	1.5
Time length of HIV diagnose (years)		
Mean (dp)	9,3 (6,1)	
Median (min - max)	8,5 (1 - 27)	
≤ 10	83	61.9
> 10	51	38.1

Table 1: *Patient demographic data, clinical data, laboratory data, therapeutic data, and neurocognitive analysis.*

with HAD, we performed the Poisson multiple regression with robust variance statistical analysis and considered significant variables with $p < 0.20$ on the bivariate analysis.

After completing the Poisson analysis, we accepted variables with $p \leq 0.05$.

We analyzed 134 adult patients selected from 1437 individuals in the UNIFESP Outpatient Infectious Disease Clinic. Most patients were male (53.7%), 45 years old (63.4%), with six or more years of education (80.6%), and heterosexual (78.4%) (Table I). Fifty percent of patients had a BMI of up to 24.5 kg/m2, and 19.4% had HT and/or DM. The median time of HIV disease was 8.5 years - from 1 to 27 years of disease diagnosis. Most people had TCD4+ lymphocytes up to 200 cells/mm3, 69.2% had the first HIV viral load lower than 100.000 copies/ml, and only one patient had an undetectable viral load at the diagnosis. During the recruitment, most patients had TCD4+ lymphocytes $\geq$ 500 cells/mm3 (58.2%) and an undetectable HIV viral load (82.1%) (Table 1).

Most patients had TCD4+ $\geq$ 500 cells/mm3 for up to 3 years (53.0%) and lower than 200 cells/mm3 for up to 1 year. Most patients received HAART for at least one year (52.2%), and in total, 91.0% of patients used HAART during HIV disease.

As for the neurocognitive evaluation, most patients had a CPE score lower than 8 (55.2%), and 85.1% had average mini-mental scores.

This statistical analysis showed a significant association between dementia and education ($p < 0.001$) and the time length of detectable HIV viral load (p=0.016) (Table 2).

The multiple analysis found that age, TCD4+ nadir, and time length of detectable HIV viral load were independently related to dementia (Table 3).

The older the patient, the higher the risk of developing dementia ($p = 0.033$). Every year of life, there is an increase of 5% in the risk of HAD regardless of TCD4+ nadir and the time length of detectable HIV viral load. However, the higher the TCD4+ nadir, the lower the HAD risk ($p = 0.030$). For each unit increase in TCD4+, there is a reduction of 0.2% in the risk of having HAD, regardless of the patient's age and time length of detectable HIV viral load.

Patients with more than two years of detectable HIV viral load had 135% more risk of developing HAD than those with less than two years of detectable viral load ($p = 0.006$), regardless of the patient's age and TCD4+ nadir.

Variables	Total	Dementia nº	Dementia %	PR	CI 95% (PR)	p
Sex						0,061
Male	72	11	15,3	1		
Female	62	18	29,0	1,90	0,97 - 3,72	
Age (years)						0,058
≤ 45	85	14	16,5	1		
> 45	49	15	30,6	1,86	0,98 - 3,53	
Education (years)						<0,001
≤ 5	26	14	53,8	1		
> 5	108	15	13,9	0,26	0,14 - 0,47	
HIV risk behavior*						0,144
Heterosexual	105	26	24,8	1		
Homosexual/Bisexual	28	3	10,7	0,43	0,14 - 1,33	
Comorbidity (HT ou DM)						0,459
No	108	22	20,4	1		
Yes	26	7	26,9	1,32	0,63 - 2,76	
Time length of HIV diagnose (years)						0,202
≤ 10	83	15	18,1	1		
> 10	51	14	27,5	1,52	0,80 - 2,89	
BMI (kg/m^2)				0,91	0,81 - 1,03	0,139
(*) one case of blood transfusion						
Nadir TCD4+ (cell/mm^3)						0,317
≤ 200	72	18	25,0	1		
> 200	62	11	17,7	0,71	0,36 - 1,39	
First HIV viral load (copies/ml)*						0,629
< 100 mil	92	19	20,7	1		
≥ 100 mil	41	10	24,4	1,18	0,60 - 2,32	
TCD4+ on recruitment (cells/mm^3)						0,930
≤ 350	34	8	23,5	1		
351 - 499	22	5	22,7	0,97	0,36 - 2,58	
> 500	78	16	20,5	0,87	0,41 - 1,85	
Viral load on recruitment						0,656
Undetectable	110	23	20,9	1		
Detectable	24	6	25,0	1,20	0,55 - 2,62	
Time length of TCD4+ <500 cells/mm^3 (years)						0,325
≤ 3	71	13	18,3	1		
> 3	63	16	25,4	1,39	0,72 - 2,66	
Time length of TCD4+ <200 cells/mm^3 (years)						0,155
≤ 1	105	20	19,0	1		
> 1	29	9	31,0	1,62	0,83 - 3,19	
Time length of detectable HIV viral load (years)						0,016
≤ 2	82	12	14,6	1		
> 2	52	17	32,7	2,23	1,16 - 4,30	
(*) one ignored data						
Time length of cART before recruitment (years)	82	15	18,3	1		0,238
≤ 1	52	14	26,9	1,47	0,77 - 2,80	
> 1						
CPR score on recruitment	74	14	18,9	1		0,398
< 8	60	15	25,0	1,32	0,69 - 2,52	
≥ 8						
Mini-mental	20	7	35,0	1		0,099
Inadequate	114	22	19,3	0,55	0,27 - 1,12	
Adequate						

RP: Prevalence Ratio

Table 2: *Prevalence ratio of dementia according to demographic data, clinical and laboratory data, therapeutic data, and neurocognitive evaluation.*

Discussion

We observed HAD prevalence of 21.6% (CI 95%: 15.0 – 29.6) in our sample, meaning that 29 patients over 134 were screened for possible HAD diagnosis. The

Variables	PR_{na}	PR_a	CI 95% (PR_a)	p
Age (years)	1,05	1,05	1,00 - 1,09	0,033
TCD4+ Nadir (cells/mm^3)	0,998	0,998	0,996 - 0,999	0,030
Time length of detectable HIV viral load (years)				0,006
≤ 2	1	1		
> 2	2,23	2,35	1,27 - 4,33	

Table 3: *Prevalence ratio of dementia according to the Poisson multiple regression with robust variance.*

international data is similar to ours, showing a 15 to 55% prevalence, depending on the country (Saylor et al., 2016). Unfortunately, there are few studies regarding HAD in Brazil. Troncoso & Conterno, 2015 did similar research and observed 52% of HAD prevalence; however, they didn't specify the inclusion or exclusion of addictive patients (alcohol and drugs). Another Brazilian research showed that HAND was prevalent in 54.1% of that specific population (Pinheiro et al., 2016), and in Recife – a Brazilian city – one more study was conducted and showed 36.5% of HAND prevalence and 13.5% of HAD (Fernandes Filho & de Melo, 2012).

Our research had more strict inclusion and exclusion criteria compared to Brazilian literature. Despite using low-sensitive neurologic tests, our population had a high prevalence of HAD, leading to an essential change in our patient care.

The independent factors associated with dementia in our study were advanced age (PRa 1.05; CI 95% 1.00 – 1.09; p = 0.033), lower TCD4+ nadir (PRa 0.998; CI 95% 0.996 – 0.999; p = 0.030), and patients with more than two years of detectable HIV viral load (PRa 2.35; CI 1.27 – 4.33; p = 0.006). These factors increase the inflammatory process in the CNS, which leads to homeostasis imbalance, changes in the cellular metabolism, and consequent cerebral tissue damage (de Almeida et al., 2006; Saylor et al., 2016; Saylor et al., 2016; Stingele et al., 2001; Zayyad & Spudich, 2015). CPE was not associated with HAD development, and we can't define specific therapy to control all types of HAND. The number of comorbidities of older patients may explain their higher risk for HAD.

Our study had barriers such as the small sample size, not being a multicenter study, and only one tracking method because these factors can reduce the chances of detecting possible patients with HAD. In addition, we did not perform lumbar punction to analyze viral load in the cerebrospinal fluid, we did not examine any brain image – such as brain computed tomography or brain magnetic resonance imaging - and we did not have a control group. Furthermore, we did not analyze or consider the treatment failures and the time frame they had blips in their viral load among participants. Moreover, this study focuses on prevalence, and the results may have false positives. All these factors can negatively impact our study. Nevertheless, we applied an easy and workable tool that can be used in clinical practice to help screen patients with HAD.

Conclusions

In conclusion, despite all the negative aspects, we found a high prevalence of HAD in our study. Advanced age, lack of HIV viral load control, and low TCD4+ nadir are risk factors associated with possible dementia development. Those findings indicate how important it is to screen for neurocognitive disorders, diagnose early, control HIV viral load, and prevent severe immunosuppression in PLHIV. These actions can provide a better life quality for PLHIV; nevertheless, we still need more studies to understand the pathogenesis, diagnosis, and treatment of HIV-associated neurocognitive disorders.

Author Contributions

Conceptualization, Daniela Pereira Lamas, Simone Barros Tenore, and Paulo Roberto Abrao Ferreira.; methodology, Daniela Pereira Lamas, Simone Barros Tenore, and Paulo Roberto Abrao Ferreira.; software, Paulo Roberto Abrao Ferreira.; validation, Paulo Roberto Abrao Ferreira, and David Salomao Lewi.; formal analysis, Paulo Roberto Abrao Ferreira.; investigation, Daniela Pereira Lamas.; resources, Paulo Roberto Abrao Ferreira.; data curation, Daniela Pereira Lamas.; writing—original draft preparation, Daniela Pereira Lamas.; writing—review and editing, Paulo Roberto Abrao Ferreira.; visualization, David Salomao Lewi.; supervision, Paulo Roberto Abrao Ferreira.; project administration, Daniela Pereira Lamas. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

PubMed, Cochrane.

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Conflicts of Interest

The authors declare no conflict of interest.

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