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SHORT COMMUNICATION

Neurocognitive evaluation using the International HIV Dementia Scale (IHDS) and Montreal Cognitive Assessment Test (MoCA) in an HIV-2 population

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Objectives

We aimed to characterize neurocognitive impairment (NI) in an HIV-2 population using an observational cross-sectional study in four Portuguese hospitals.

Methods

Adult HIV-2-infected patients were included. Montreal Cognitive Assessment Test (MoCA) and International HIV Dementia Scale (IHDS) scales were applied for screening of NI. Patient Health Questionnaire-9 (PHQ-9) and Instrumental Activities of Daily Living (IADL) scales were used for assessment of depression and functionality. A multivariate analysis was performed to assess for risk factors for NI.

Results

Eighty-one patients were included, 50.6% of African origin (n = 41) and 49.4% of Portuguese origin (n = 40). The MoCA scale showed alterations in 81.5% of patients (100% of migrants *vs.* 62.5% of non-migrants, $P < 0.001$) and the IHDS scale showed alterations in 42%. Both scales were altered simultaneously in 35.8%. Variables independently associated with NI were age [odds ratio (OR) = 0.885] and migrant status (OR = 9.150).

Conclusions

Neurocognitive impairment (both scales altered) was present in 35.8%, which is comparable to what is described for HIV-1. The MoCA performed worse in the migrant population and might not be applicable in this setting.

Keywords: HIV-associated neurocognitive disorder, HIV-2, International HIV Dementia Scale (IHDS), Montreal Cognitive Assessment Test (MoCA), neurocognitive impairment

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Background

HIV-associated neurocognitive disorders (HAND) comprise a wide clinical spectrum, ranging from psychomotor retardation to mnesic deficit, non-specific changes in executive functions, apathy, abulia and/or reduction of affective resonance. Symptoms develop insidiously and affect mostly basal nuclei and white matter [1,2].

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The current definition based on the Frascati criteria divides HAND into three separate categories, by ascending order of dysfunction and impairment of daily activities: asymptomatic neurocognitive impairment, mild neurocognitive disorder and HIV-associated dementia [1].

It is estimated that 25–46% of patients with untreated HIV infection will progress to HAND [3,4]. Since the introduction of effective antiretroviral therapy (ART), a clear reduction in severe forms of HAND has been seen. However, milder presentations of neurocognitive impairment (NI) have been increasingly described, even in patients with sustained viral suppression [3].

The gold standard for diagnosis of HAND is formal neuropsychological cognitive testing. However, for practical purposes, tools such as the International HIV Dementia Scale (IHDS) and the Montreal Cognitive Assessment (MoCA) have been validated for screening of NI in HIV populations [5,6].

HIV-2 is a neurotropic virus [7], but little is known about its pathogenicity on the central nervous system. It is acknowledged that HIV-2 mainly infects macrophages and microglia, apparently sparing neurons, astrocytes and oligodendrocytes [8]. However, the possible clinical repercussions of this phenomenon and the prevalence of NI in the HIV-2 population have not yet been accurately described.

In this context, we aimed to quantify and characterize NI in patients with HIV-2 infection and hence have a better insight into the neurological repercussions of HIV-2 infection.

Methods

We used an observational, cross-sectional, multicentric study including HIV-2 infected adult patients from four Portuguese hospitals. Patients aged 18 years or over with HIV-2 infection were included and follow-up was done in one of the study centres. The following were excluded: patients with HIV-1 co-infection, those participating in a clinical trial during this study period, those with NI attributable to other previously documented causes (such as cerebrovascular disease, dementia or other neurological conditions), those with clinical alterations suggestive of active psychiatric disease, those who were active drug users or under opioid substitution treatment, those who could not read, write or understand the Portuguese language or those with other clinical alterations that limited the applicability of the any of the study scales.

Data were collected between 30 November 2016 and 31 May 2017. Demographic data (gender, probable mode of acquisition of HIV infection, education, place of birth of self and parents, employment status) and data on HIV infection and co-infections (current and initial viral load, current and nadir CD4 cell count, ART regimen and duration, Central nervous system Penetration Effectiveness (CPE) score, co-infections with hepatitis B, hepatitis C, HTLV, syphilis and time since diagnosis) were collected from medical records.

The MoCA and IHDS scales were applied for screening of NI. These scales have previously been validated in HIV populations. The validated Portuguese language versions of these scales were used. Scores < 26 points on MoCA and < 10 points on IHDS were considered altered, such as has been validated for the Portuguese language versions.

Neurocognitive impairment, meaning the presence of altered screening tests suggestive of HAND, was defined in two ways: both as an altered result in either scale and as an altered result in both scales simultaneously. A separate analysis using each definition was performed.

Patient Health Questionnaire-9 (PHQ-9) and Instrumental Activities of Daily Living (IADL) scales were used to assess depression and patient functional capacity.

All scales were applied during the appointments. If they had been applied previously (in the last 18 months), those values were used. Scales were applied by one investigator from each participating centre (FA, RT, DT, MG), who were trained in this process in a collective 3-h session.

Approval from each participating institution's ethical commission and informed consent from each patient were obtained.

Sample size was calculated assuming an error margin of 7% for an expected prevalence of NI of 35% [3,4]. Descriptive analysis was used to describe sociodemographic and clinical characteristics of patients. Scale results were analysed through mean and confidence interval to 95%. Comparisons between patients with and without NI in one or both scales were made using χ^2 test. Continuous variables were compared using Student's *t*-test.

The association between NI and biodemographic and clinical variables was analysed. For this purpose, two-step binary logistic regression was used to estimate the probability of a binary response (NI) using biodemographic and clinical variables as predictors. Variables with statistical significance in the univariate analysis were included in the regression model. For the multivariate analysis, NI was defined as an altered result in either of the scales.

Patients whose country of birth or whose parents' country of birth was not Portugal were classified as patients from a migrant population and were predicted to be present in a significant proportion in our sample, regarding the referral areas of the participating centres and our country's historical context. Due to expected cultural and linguistic background differences, this population was analysed as a separate subgroup.

Results

Our study included a total 81 patients, 50.6% of African origin (n = 41) and 49.4% of Portuguese origin (n = 40). Migrant patients (African origin) were originally from Guinea-Bissau (n = 37; 45.7%) or Cape Verde (n = 4; 4.9%).

Sociodemographic data and characteristics of HIV infection in the global sample and in migrant and non-

migrant populations are given in Table 1. The migrant population included more unemployed patients (43.9% *vs.* 2.5%), fewer retired patients (9.8% *vs.* 52.5%) and more patients with undetectable viral load on diagnosis (68.3% *vs.* 48.1%). Mean duration of diagnosis (6.3 years) and mean duration of ART (4.7 years) were both lower in the migrant population than in the non-migrant population (17.9 and 13.3 years, respectively). IADL was more often altered in the non-migrant population (41.2% *vs.* 17.5%).

No significant differences were present between non-migrant and migrant patients regarding gender, age, education level, CD4 nadir or ART CPE score.

Table 1 Sample description and scale results

	Global sample	Migrant population	Non-migrant population	*P*
Sample size [*n* (%)]	81 (100)	41 (50.6)	40 (49.4)	–
Female gender [*n* (%)]	46 (56.8)	23 (56.1)	23 (57.5)	0.89
Age (years) [mean (SD)]	54.4 (11.6)	52.0 (9.7)	56.8 (13.0)	0.068
HIV transmission risk [*n* (%)]				
Heterosexual	65 (80.2)	40 (97.6)	25 (62.5)	0.001
Homosexual	1 (12)	0	1 (2.5)	
IV drug use	0	0	0	
Blood transfusions	14 (17.3)	1 (2.4)	13 (32.5)	
Vertical	1 (1.2)	0	1 (2.5)	
Education [*n* (%)]				
Cannot read or write	4 (4.9)	4 (9.8)	0	0.123
< 4 years	24 (29.6)	12 (29.3)	12 (30.0)	
5–9 years	30 (37.0)	16 (39)	14 (35.0)	
10–12 years	11 (13.6)	5 (12.2)	6 (15.0)	
College education	6 (7.4)	3 (7.3)	3 (7.5)	
Unknown	6 (7.4)	1 (2.4)	5 (12.5)	
Professional situation [*n* (%)]				
Employed	32 (39.5)	18 (43.9)	14 (45.0)	< 0.001
Unemployed	19 (23.5)	18 (43.9)	1 (2.5)	
Retired	25 (30.9)	4 (9.8)	21 (52.5)	
Homemaker	2 (2.5)	1 (2.4)	1 (2.5)	
Student	1 (1.2)	0	1 (2.5)	
Unknown	2 (2.5)	0	2 (5.0)	
Time since diagnosis (years) [mean (SD)]	11.9 (8.8)	6.3 (5.4)	17.9(7.7)	< 0.001
T CD4+ nadir (cells/μL) [mean (SD)]	321.0 (244.2)	373.8 (247.1)	266.7 (231.9)	0.054
Current CD4+ cell count (cells/μL) [mean (SD)]	562.7 (317.7)	540.3 (242.8)	585.5 (381.5)	0.526
Viral load at diagnosis (copies/mL) [mean (SD)]	3905.8 (13 968.3)	1727.4 (5685.6)	6685.2 (19 927.6)	0.154
Undetectable viral load at diagnosis [*n* (%)]	39 (48.1)	28 (68.3)	11 (27.5)	0.02
Current viral load (copies/mL) [mean (SD)]	729.6 (5132.2)	105.0 (554.4)	1369.9 (7272.1)	0.270
Undetectable current viral load [*n* (%)]	70 (86.4)	35 (85.4)	35 (87.5)	0.779
Under ART [*n* (%)]	60 (74)	28 (68.3)	32 (80.0)	0.229
Duration of ART (years) [mean (SD)]	9.3 (7.7)	4.7 (3.2)	13.3(8.3)	< 0.001
CPE score [*n* (%)]				
Not under ART	21 (25.9)	13 (31.7)	8 (20)	0.575
< 8	28 (34.6)	13 (31.7)	15 (37.5)	
Between 8 and 9	26 (32.1)	13 (31.7)	13 (32.5)	
Higher than 9	6 (7.4)	2 (4.9)	4 (10.0)	
HCV chronic infection [*n* (%)]	5 (6.2)	1 (2.4)	4 (10)	0.157
HVB chronic infection [*n* (%)]	6 (7.4)	4 (9.8)	2 (5)	0.414
HTLV infection [*n* (%)]	1 (1.2)	1 (2.4)	0	0.037
Positive VDRL [*n* (%)]	3 (3.7)	1 (2.4)	2 (5)	0.542
Altered PHQ-9 [*n* (%)]	41 (56.1%)	22 (55%)	19 (57.5%)	0.825
Altered IADL [*n* (%)]	21 (28.4%)	7 (17.5%)	14 (41.2%)	0.024
Any scale with altered scores (MoCA or IHDS) [*n* (%)]	71 (87.7)	41 (100.0)	30 (75.0)	< 0.001
Both scales with altered scores (MoCA and IHDS) [*n* (%)]	29 (35.8%)	17 (41.5%)	12 (30%)	0.282
MoCA score mean (SD)	21.5 (5.0)	18.9 (5.1)	24.4 (3.0)	< 0.001
Altered MoCA score [*n* (%)]	66 (81.5)	41 (100)	25 (62.5)	0.001
IHDS score mean (SD)	10 (2)	9.9 (2.4)	9.9 (2.36)	0.524
Altered IHDS score [*n* (%)]	34 (42%)	17 (41.5%)	17 (42.5%)	0.925
Discordant scales	42 (51.9%)	24 (58.5%)	18 (45%)	0.159

ART, antiretroviral therapy; CPE, Central Nervous System Penetration Efectiveness; IHDS, International HIV Dementia Scale; HTLV, human T-cell leukaemia virus; VDRL, Venereal Diseases Research Laboratory syphilis serology; PHQ-9, Patient Health Questionnaire-9; IADL, Instrumental Activities of Daily Living; MoCA, Montreal Cognitive Assessment Test.

Table 2 Multivariate analysis for neurocognitive impairment

Independent variables in the model	Exp(*B*)	95% confidence interval		*P*
		Lower	Upper	
Gender	4.268	0.881	20.672	0.071
Age	0.885	0.813	0.965	0.005
Migrant	9.150	1.069	78.352	0.043
Education	0.258	0.063	1.052	0.059
PHQ-9	2.505	0.565	11.118	0.227
IADL	1.053	0.221	5.018	0.948
Disease duration	0.941	0.848	1.044	0.251
CD4 nadir	1.001	0.997	1.006	0.539
CD4 present	0.999	0.996	1.002	0.366
ART	0.764	0.125	4.596	0.764

ART, antiretroviral therapy; PHQ-9, Patient Health Questionnaire-9; IADL, Instrumental Activities of Daily Living.
Variables entered on step 1: CD4_nadir, CD4 present, disease duration, ART.

Regarding neurocognitive scale results (Table 1), the overall proportion of neurocognitive impairment, defined as an altered result in either the MoCA scale or the IHDS scale, was 87.7%. The MoCA scale showed alterations in 81.5% of patients (100% of migrants *vs.* 62.5% of non-migrants, $P < 0.001$) and the IHDS scale was altered in 42%. Both scales were altered simultaneously in 35.8%.

Comparing to patients with normal IHDS score, the altered IHDS score subgroup included fewer women (41.2% *vs.* 68.1%), with higher median age (61.21 *vs.* 49.62 years). Most patients with altered IHDS score were either unemployed (29.4%) or retired (50%) and had lower levels of education.

Patients with altered MoCA were mostly from the migrant population (62.1% migrant *vs.* 37.9% non-migrant) and had been diagnosed with HIV infection more recently (10.46 *vs.* 18.71 years since diagnosis). There was a higher proportion of employed and unemployed patients and a lower proportion of retired patients in this subgroup.

In 42 patients (51.9%), scale results were non-concordant (five with abnormal IHDS and normal MoCA scores and 37 with abnormal MoCA and normal IHDS scores). Cohen's kappa index between scale results was 0.21.

Applying a binary logistic regression, variables independently associated with cognitive impairment were age [odds ratio (OR) = 0.885 (95% CI 0.813–0.965), $P = 0.005$] and migrant status [OR = 9.150 (1.069–78.352), $P = 0.043$] (Table 2).

Discussion

Both scales used in our study (MoCA and IHDS) have previously been utilized for the screening of HAND. IHDS has been validated in several contexts and appears to have low sensitivity but good specificity. It is mostly useful for the diagnosis of more advanced forms of dementia and might display lower sensitivity in milder forms of cognitive impairment [9–12].

The MoCA has previously displayed higher sensitivity and poor specificity in this context and might perform better in the diagnosis of milder forms of neurocognitive impairment [9,13,14]

In our sample, after a mean time of 11.9 years since HIV-2 diagnosis, neurocognitive impairment (defined as an alteration on either the MoCA or IHDS scale) was present in 87.7% of patients. In 35.8% of patients, both MoCA and IHDS scales were altered. Discrepancy between the two scales was widely present, with significantly more patients having altered MoCA scale results.

When NI is defined as an alteration in both scales simultaneously, the prevalence in our HIV-2 cohort was comparable to what is described for HIV-1 (25–46%) [3,4]. However, when NI was defined as an alteration on either scale, the results in our population vastly exceeded those figures. The overestimation of NI in HIV patients when MoCA is used has been described as a reason for caution in applying this scale, which on its own might not be a good tool for screening in this context [15]. We used a cut-off of 26 points. It has been proposed that lower cut-off points might increase accuracy. However, independently of the chosen cut-off, MoCA accuracy remains below 70% [6].

Migrant status was an independent risk factor for NI in our multivariate analysis. This can probably be explained by an overestimation of NI in migrant populations by MoCA, as IHDS was equally altered among migrants and non-migrants. Old age was also an independent risk factor for NI and was evenly distributed between the migrant and non-migrant subgroups. The PHQ-9 test was altered in over half of the patients, suggesting that some degree of depression could have been present in a significant proportion of our sample. Although a confounding effect of depression on neurocognitive performance might be expected, it was not an independent risk factor for NI in our analysis. IDLA varied between groups but was less frequently altered in the migrant population and also did not show significance in the multivariate analysis.

Previous data, including studies in Africa and in populations of African origin, suggested that MoCA might not be suitable for populations with different cultural backgrounds from the population for which the questionnaire was validated [16–19].

Therefore, the MoCA scale was altered in a proportion of patients far larger than what would be expected in an HIV-1 population, and mostly in migrant patients.

Although the discrepancy in MoCA results seems to derive from its lower applicability in migrant populations,

this hypothesis would require validation using formal neuropsychological testing or by comparison with clinical neurocognitive data.

One previous study applied IHDS in a sample of 22 HIV-2 infected patients and found similar mean scores as in the control seronegative population (eight in both) [20]. In our literature review, we found no other studies evaluating the prevalence of NI in HIV-2 patients. It was also impossible to find studies discriminating the prevalence of NI in migrant and non-migrant populations in a developed country.

Limitations of our study include a small sample size, which nevertheless mirrors the global prevalence of HIV-2 and, as stated, is the largest sample of HIV-2 patients evaluated for this purpose. Despite this, we tried to limit confounding by excluding all patients with acute or chronic diseases with a potential impact on test performance. Also, even after excluding patients who could not understand the Portuguese language, a high proportion of them were from a distinct cultural and linguistic background, which might have limited the applicability of the scales.

In addition, the absence of a comparator arm limits the interpretation of our results, which we tried to contextualize by comparison with historical cohorts for HIV-1.

Furthermore, even if validated scales are used to screen for HAND, these should be accompanied by neuropsychological testing, functional status assessment and exclusion of other causes of NI [1], which were not performed in our study due to practical issues. In particular, neuropsychological testing would be essential to serve as a gold standard for diagnosis of HAND and to assess its true prevalence in this disease, for which further studies are needed.

Finally, inter-user variability in the application of the scales might have hampered global results. However, all physicians applying the scales had a prior debriefing and clarification session on the matter.

In conclusion, neurocognitive impairment was present in 87.7% of the HIV-2 patients in our series, when defined as an alteration in either MoCA or IHDS. By contrast, if NI was defined as alterations in both scales, it was present in 35.8%, similar to what is described for HIV-1 populations. Scales were discordant and MoCA results were significantly worse in the migrant population. Old age was also an independent risk factor for altered scale results.

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Author contributions

All authors conceived of and designed the study. FA, MG and RT applied the scales. FA, AM, DT, MA MG and RT carried out the statistical analyses. All authors contributed to writing and review of the manuscript.

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