Cognitive function and drivers of cognitive impairment in a European and a Korean cohort of people living with HIV

Keywords: Cognitive impairment; HIV; Cognitive performance; People living with HIV

Short title: Cognitive function in European and Korean PLWH

Abstract

Background: Although cognitive impairments are still prevalent in the current cART era, limited investigations compared the prevalence of cognitive disorder in PLWH and its determinants from different region and ethnicity.

Methods: We compared cognitive performance across six domains using comparable batteries in 134 PLWH aged ≥45 years from the COBRA study (Netherlands, UK), and 194 PLWH aged ≥18 years from the NeuroAIDS Project (South Korea). Cognitive scores were standardized and averaged to obtain domain and global T-scores. Associations with global T-scores were evaluated using multivariable regression and the ability of individual tests to detect cognitive impairment (global T-score ≤45) was assessed using the area-under-the-receiver-operating-characteristic curve (AUROC).

Results: The median (IQR) age of participants was 56 (51, 62) in COBRA (88% white ethnicity, 93% male) and 45 (37, 52) in NeuroAIDS (100% Korean ethnicity, 94% male). The rate of cognitive impairment was 18.8% and 18.0% respectively (p=0.86). In COBRA, black-African ethnicity was the factor most strongly associated with cognitive function (11.1 (7.7, 14.5) lower scores vs. white ethnicity, p<0.01), whereas in NeuroAIDS only anemia (-1.2 (-2.6, 0.3), p=0.12) was weakly associated, after age and years of education. Cognitive domains most associated with cognitive impairment were attention (AUROC=0.86) and executive function (AUROC=0.87) in COBRA and processing speed (AUROC=0.80), motor function (AUROC=0.78) and language (AUROC=0.78) in NeuroAIDS.

Conclusions: Two cohorts of PLWH from different geographical regions report similar rates of cognitive impairment but different risk factors and cognitive profile of impairment.

Introduction

In the combination antiretroviral therapy (cART) era, cognitive impairment in people living with HIV (PLWH) remains prevalent with reported rates varying from 19% to 74%, most of which were derived from European and North American populations (1-3). Cognitive data on Asian populations of PLWH are sparse and their results vary across diverse regions. Studies on Asian populations of PLWH reported a varying prevalence of cognitive impairment, ranging from 25% to 75% (4-9) (Supplementary Table 1).

However, except a few multinational studies that included some Asian regions, direct comparisons between European and Asian cohorts are lacking (10, 11). Findings on cognitive performances from European countries may not be generalizable to Asian populations due to differences in socioeconomic, cultural and lifestyle factors that may influence cognitive performance. International studies would enhance our understanding of issues such as HIV-associated cognitive disorders and help in the development of specific international programmes. Comparing factors associated with cognitive disorders across ethnically and culturally different regions of the world would help clinicians in identifying appropriate targeted interventions that are relevant in the settings in which they operate.

In the Republic of Korea, there were 1191 new HIV diagnosis in 2017 with the cumulative number of confirmed HIV infections exceeding the 12 thousands units. With all the costs related to testing and treatment of PLWH, including antiretroviral drugs, covered by the national health insurance service and the governmental budget, the Republic of Korea has one of highest rates of diagnosed PLWH getting sustained cART worldwide (12).

We hypothesized that in the current cART era, even in resource-rich settings, the prevalence of cognitive disorder and its determinants could vary by geographical region. In this study we aimed to compare the proportion and risk factors of cognitive impairment in a Western European and a South Korean cohort using similar neuropsychological tests, and to assess the ability of each cognitive test to discriminate between those with and without cognitive impairment in the two cohorts.

Patients and Methods

The COmorBidity in Relation to AIDS (COBRA) cohort was designed to investigate the link between HIV and age-associated non-communicable comorbidities, including cognitive impairment. The study recruited 134 PLWH aged ≥45 years, on cART and with plasma HIV RNA <50 copies/mL for ≥12 months, from outpatient HIV clinics in Amsterdam (the Netherlands) and London (UK) as described (13).

The Korean NeuroAIDS project launched to evaluate the prevalence of cognitive impairment in Korean PLWH. It recruited 194 PLWH aged ≥18 years from two South Korean university hospitals (Severance Hospital and Korea University Guro Hospital) (14).

Cognitive testing

Cognitive performances were assessed in the two cohorts using a comparable battery covering six cognitive domains (Supplementary Table 2). Scores were standardized into T-scores (mean=50, standard deviation=10) using population-specific normative data accounting for age, gender, ethnicity and educational level, as appropriate. Within each cognitive domain, individual T-scores were averaged to calculate the domain T-score and across domains to calculate the global T-score. For all T-scores, higher scores

indicate better cognitive function. Cognitive impairment was defined by an overall T-score ≤45 (i.e. ≥0.5 standard deviations below the mean normative score) and also using the HIV-Associated Neurocognitive Disorders (HAND) criteria (15), for which the average domain scores were used. Briefly, according to the HAND criteria, an individual was classified as cognitively impaired when at least two domains were one or more standard deviations below the normative mean. Determinants of cognitive function were assessed with respect to the global T-score (as continuous outcome) to overcome the intra-individual variability of binary classification of cognitive impairment (16, 17).

Statistical analysis

We compared the proportion of cognitive impairment in the two cohorts using the Chi-square test. Associations with overall cognitive function (as indicated by the global T-score) were evaluated separately in the two cohorts using linear regression. Factors considered included: socio-demographic characteristics (age, gender, ethnicity and years of education), body mass index (BMI), anaemia (blood hemoglobin ≤13 g/dL for men, ≤12 g/dL for women) and HIV-parameters (route of acquisition, current and nadir CD4 count, CD4:CD8 ratio, time since diagnosis, prior AIDS-defining event). Those factors that were associated with cognitive function in univariable analyses (5% significance) were selected for simultaneous inclusion in a multivariable model. The discriminative ability of individual cognitive tests and domain T-scores to detect cognitive impairment was assessed using the area-under-the-receiver-operating-characteristic (AUROC) curve (0.5: discriminative ability no better than chance; 1: perfect discriminative ability).

In order to allow a fairer comparison of the two cohorts we ran sensitivity analyses comparing the proportion of cognitive impairment and determinants of cognitive function in the two cohorts only restricting to participants with HIV RNA <50 copies/mL (i.e. all COBRA participants and 72% of NeuroAIDS participants).

Results

Characteristics of the two cohorts

A total of 134 and 194 participants from COBRA and NeuroAIDS, respectively, were evaluated. COBRA participants were composed of white (88%) and black African (12%) ethnicity, while all NeuroAIDS participants had Korean ethnicity. Median age (IQR) differed between the two cohorts [56 (51, 62) vs 45 (37, 52) years, respectively, $p<0.01$]. In the NeuroAIDS cohort 89.7% of participants were on cART and 72% had a HIV RNA <50 copies/mL, while all COBRA PLWH were on suppressive cART (Table 1).

Table 1: Characteristics of PLWH recruited in the COBRA and NeuroAIDS studies

Median (IQR) or n (%)	**COBRA (n=134)**	**NeuroAIDS (n=194)**	***p***
Age [years]	56 (51, 62)	45 (37, 52)	<0.01
Male	125 (93%)	182 (94%)	0.85
Ethnicity			<0.01
White	118 (88%)	0 (0%)	
Black-African	16 (12%)	0 (0%)	
Korean	0 (0%)	194 (100%)	
Likely route of HIV transmission			<0.01
MSM	115 (86%)	102 (53%)	
Heterosexual sex	15 (11%)	53 (27%)	
Years of education	14 (13, 16)	13 (12, 16)	0.23
BMI [kg/m^2]	24.6 (22.6, 27.4)	22.5 (20.5, 24.4)	<0.01
Anemia	10 (7%)	33 (17%)	<0.01
Hepatitis B co-infection	7 (3%)	9 (5%)	0.81
Hepatitis C co-infection	5 (2%)	6 (4%)	0.75
CD4 count [cells/µL]	618 (472-806)	477 (323, 607)	<0.01
CD4:CD8 ratio	0.84 (0.60, 1.12)	0.55 (0.35, 0.85)	<0.01
Current cART			<0.01
No treatment	0 (0%)	20 (10%)	
2 NRTIs + PI	43 (32%)	104 (54%)	
2 NRTIs + NNRTI	55 (41%)	49 (25%)	
2 NRTIs + II	5 (4%)	12 (6%)	

3 NRTIs	2 (1%)	3 (2%)	
Other	29 (22%)	6 (3%)	
HIV RNA <50 copies/mL	134 (100%)	140 (72.2%)	<0.01
Time since HIV diagnosis [years]	15.0 (9.1, 20.0)	5.8 (2.3, 8.2)	<0.01
Prior AIDS	42 (31%)	55 (28%)	0.56
Nadir CD4 count [cells/μL]	180 (90, 250)	169 (69, 273)	0.78

MSM: man having sex with man; BMI: body-mass index; Hb: hemoglobin; cART: combination antiretroviral therapy; NRTI: nucleoside reverse-transcriptase inhibitor; PI: protease inhibitors; NNRTI: non-nucleoside reverse-transcriptase inhibitor; II: integrase inhibitor; Anemia is defined by Hb ≤13 g/dL for men and Hb ≤12 g/dL for women; hepatitis B co-infection defined as detectable HBV surface antigen; hepatitis C co-infection defined as detectable HCV RNA

Proportion of cognitive impairment

The median (IQR) global T-score was 51.2 (46.0, 54.8) and 50.7 (47.1, 54.0) in COBRA and NeuroAIDS respectively (p=0.21). The proportion of cognitive impairment was comparable in both cohorts (18.8% vs. 18.0%, p=0.86). When cognitive impairment was assessed by the HAND criteria, the proportion of cognitive impairment was 17.3% in COBRA and 16.0% in NeuroAIDS (p=0.10).

Factors associated with cognitive function

In univariable analysis, anemia was significantly associated with poorer global T-scores in COBRA (p=0.01) and near significantly in NeuroAIDS participants (p=0.05, Table 2). Female gender (p=0.01), black African ethnicity (p=0.01), HIV acquisition via heterosexual sex (p<0.01) and high BMI (p=0.04) were all linked to poorer global T-scores in COBRA participants. In NeuroAIDS participants, in addition to anemia, age (p<0.01) and years of education (p=0.01) were significantly associated with global cognitive scores.

In multivariable analysis, only black African ethnicity remained significantly associated with global cognitive function among COBRA participants with, on average, 11.1 (7.7, 14.5) point lower scores compared to PLWH of white ethnicity (p<0.01). Neither gender, route of HIV transmission nor BMI were significantly associated with cognitive scores independently of ethnicity (Table 2). In the NeuroAIDS cohort, older age and fewer years of education were independently associated with poorer global T-scores (p<0.01 for each); the evidence for an association between cognitive scores and anaemia was only weak (p=0.12), after accounting for these factors.

Table 2: Regression coefficients from linear regression to predict the global T-score in COBRA and NeuroAIDS PLWH

Risk factor	COBRA (n=134)		NeuroAIDS (n=194)	
	coeff. (95% CI)	**p**	**coeff. (95% CI)**	**p**
Univariable analysis (one factor at the time)				
Age [per 10 years]	0.3 (-1.2, 1.7)	0.73	1.2 (0.6, 1.6)	<0.01
Male vs Female	6.1 (1.9, 10.3)	0.01	-1.4 (-3.8, 1.1)	0.28
Black-African vs white	-10.9 (-13.6, -8.1)	0.01	N/A	N/A
Likely route of HIV transmission				
Heterosexual vs MSM	-5.8 (-9.1, -2.5)	<0.01	-0.4 (-1.8, 1.0)	0.54
Other vs MSM	-1.8 (-7.9, 4.3)	0.56	-0.2 (-1.9, 1.7)	0.82
Years of education [per year]	0.2 (-0.2, 0.6)	0.37	0.2 (0.04, 0.4)	0.01
BMI [per 5 kg/m^2]	-1.3 (-2.6, -0.04)	0.04	0.4 (-0.4, 1.2)	0.43
Anemia (yes vs no)	-5.0 (-8.9, -1.2)	0.01	-1.5 (-2.9, -0.03)	0.05
CD4 count [per 100 cells/μL]	0.2 (-0.4, 0.7)	0.55	-0.03 (-0.3, 0.2)	0.80
CD4:CD8 ratio	-0.2 (-2.4, 2.0)	0.84	0.2 (-0.6, 1.1)	0.84
Time since HIV diagnosis [per 10 years]	0.1 (-0.03, 0.2)	0.12	0.1 (-0.1, 0.3)	0.43
Prior AIDS (yes vs no)	-1.9 (-4.2, 0.4)	0.11	-0.2 (-1.5, 1.1)	0.75
Nadir CD4 count [per 100 cells/μL]	0.5 (-0.2, 1.3)	0.15	-0.1 (-0.6, 0.3)	0.55
Multivariable analysis				
Male vs Female	-0.2 (-6.0, 5.7)	0.96		
Black-African vs white	-11.1 (-14.5, -7.7)	<0.01		
Likely route of HIV transmission				

Heterosexual vs MSM	0.3 (-4.5, 5.0)	0.91		
Other vs MSM	0.2 (-5.3, 5.6)	0.96		
BMI [per 5 kg/m^2]	-0.5 (-1.7, 0.7)	0.37		
Anemia (yes vs no)	1.2 (-2.8, 5.3)	0.55	-1.2 (-2.7, 0.2)	0.12
Age [per 10 years]			0.6 (0.1, 1.3)	<0.01
Years of education [per year]			0.7 (0.5, 0.9)	<0.01

Sensitivity analysis: only PLWH with HIV RNA < 50 copies/mL

The median (IQR) global T-score in the 140 (72.2%) NeuroAIDS PLWH with HIV RNA <50/copies/mL was 50.7 (47.9, 54.1) and did not differ significantly from that of COBRA PLWH (p=0.45). The proportion of cognitive impairment, defined as an overall T-score ≤45 and using the HAND criteria, was 14.3% and 12.1%, respectively, similar to that observed in COBRA PLWH (p=0.32 and p=0.23, respectively).

In multivariable analysis involving NeuroAIDS PLWH with HIV RNA <50/copies/mL, age [regression coefficient (95% CI): 0.5 (0.1, 0.9) per 10-years] and years of education [regression coefficient (95% CI): 0.7 (0.4, 0.9) per year] were significantly associated with global T-score, (p=0.04 and p<0.01, respectively). The association of anemia was weak [regression coefficient (95% CI): -1.0 (-3.1, 1.1)] and did not reach statistical significance (p=0.18).

Discriminative ability of cognitive impairment screening

In COBRA participants the ability to discriminate between individuals with and without cognitive impairment was highest for the Trail-Making test-B (executive function: AUROC [95% CI] 0.88 [0.82, 0.93]). Other tests of executive function (AUROC

between 0.80 and 0.81) and tests of attention (AUROC between 0.81 and 0.84) also had high discriminative ability among COBRA PLWH (Supplementary Table 3). Among NeuroAIDS participants, the WAIS-III Digit-Symbol test (processing speed: AUROC [95% CI] 0.80 [0.73, 0.86]), the Grooved pegboard (motor function: 0.78 [0.71, 0.86]) and the WAIS III Vocabulary test (language: 0.78 [0.71, 0.84]) had the highest discriminative ability.

When considering domain T-scores, executive function and attention domain T-scores had the highest discriminative ability in COBRA participants (AUROC [95% CI]: 0.87 [0.81, 0.94] and 0.86 [0.80, 0.93], respectively) with other domains reporting AUROC between 0.79 (language) and 0.66 (motor function). Among NeuroAIDS PLWH, the processing speed, motor function and language domains ranked as the best discriminators between PLWH with and without cognitive impairment (AUROC [95% CI]: 0.80 [0.73, 0.88], 0.78 [0.71, 0.86] and 0.78 [0.71, 0.84], respectively). Lower AUROC were found for the other domains (attention: 0.75; executive function: 0.73; and memory: 0.75).

Discussion

We observed a similar rate of cognitive impairment in two cohorts of PLWH from different geographical regions. Participants in the two cohorts differed culturally and ethnically but were both recruited in resource-rich settings with wide access to cART. Despite the similar rate, there were differences between the cohorts in terms of risk factors and most affected domains: in COBRA participants, the domains most affected were attention and executive function, while motor function, information processing speed and language were most affected in Korean NeuroAIDS participants.

The prevalence of cognitive impairment in the previously published article from the Korean NeuroAIDS cohort was greater than reported here. Ku et al. (14) used the HAND definition with each domain considered as impaired when at least one test within that domain was ≥1 standard deviations below the norm. This could lead to an overestimate of the prevalence (18) as suggested previously (16, 17) and contrasts with the approach used here, where the average of scores within a domain was used. Given the lack of a gold standard to define cognitive impairment, its prevalence is very sensitive to the methods used (16, 17), with ongoing debate on the optimal methodology (19). Here we applied criteria to define cognitive impairment using the global T-score as described previously, and looked at associations with overall cognitive function, rather than being classified as impaired or not (20).

In this study, no HIV-specific or other comorbidity-related risk factors were significantly associated with cognitive impairment, with only anemia reaching marginal significance in the Korean cohort. Anemia is related to dementia in elderly HIV-negative populations and also to cognitive impairment among PLWH in the cART era (21, 22). Proposed mechanisms include HIV-associated systemic inflammation and/or neuroinflammation, failure of brain oxygenation and/or mitochondrial function by the altered cellular iron metabolism or as a non-specific marker of other pathology that also adversely affects cognitive function (22). There is a paucity of literature on the interplay between ethnicity and anaemia on cognitive impairment in PLWH. The Veterans Aging Cohort Study (VACS) index, which includes anemia as one of the factors to predict all-cause mortality in PLWH, showed association with concurrent risk for cognitive impairment (23). However when considered in conjunction with ethnicity, VACS scores were significantly associated with deterioration of global cognition only among Non-

Hispanic whites and African Americans and not among Hispanics (24). Interestingly, in the Korean cohort, older age was associated with better cognitive function. Whilst cognitive function usually deteriorates with age, older PLWH tend to have a better virological response, likely due to better adherence, than their younger counterparts (25, 26) which may explain our findings.

Whilst the rates of cognitive impairment in the two groups are comparable, cognitive tests and domains that best predict cognitive impairment differed. Intriguingly, whereas tests for attention and executive function had higher AUROC in the COBRA cohort, tests of motor function, information processing speed and language had higher AUROC in the NeuroAIDS cohort. Heaton et al. observed deficits in motor, dexterity speed, information processing speed, and verbal fluency among PLWH in the pre-cART era, but deficits of learning and executive function in the cART era (27). They interpreted this phenomenon as a shifting pattern of cognitive impairment from subcortical and white matter to cortical lesion. Although HIV-associated brain neural damages show lack of regional specificity, preferential disruption in the fronto-striato-thalamocortical loop has been suggested (28). For revelation of mechanisms related with this discrepancy in the current cART era, further functional and structural neuroimaging or biomarker studies are justified to explain our results.

Whilst a notable expansion of the number of studies on cognitive impairment in non-Western populations of PLWH has been observed, there remains a paucity of studies in Asian regions (29). Using different criteria and neuropsychiatric tests, the few existing studies have produced varying prevalence estimates (25-43%, Supplementary Table 1). The studies have also varied with regards to the accessibility to cART and treatment

strategies, even among studies conducted in the same era, so the prevalence and associated risk factors should be read in those contexts.

This study has limitations. Firstly, the two cohorts recruited a selected group of PLWH willing to participate in the respective study and undergo all the clinical examinations. Whilst at least one of the cohorts (COBRA) has been shown to be representative of larger cohorts of PLWH in the respective countries (13), the proportion and determinants of CI reported here might differ from those that would have been observed in random samples of PLWH in The Netherlands/UK and Korea. Secondly, in this comparative descriptive study, subjects from the two cohorts were not recruited under the same inclusion criteria and some baseline characteristics were not equally distributed across the two cohorts. These include age, duration of HIV infection, viral suppression and cART regimen, which all may have contributed to differences in the domains affected in the two cohort. Sensitivity analysis showed no difference when comparing only PLWH with suppressed viremia from both cohorts. On the other hand, duration of HIV infection is also strongly related to treatment history; PLWH with longer duration of infection are more likely to have been treated with earlier generations of cART drugs, generally considered to have the greatest toxicities. Moreover, PLWH in the NeuroAIDS cohort had a shorter duration of HIV infection but more advanced immune suppression (lower CD4 count and CD4:CD8 ratio), suggesting higher rates of late HIV diagnosis, which may also contribute to cognitive problems (30). The two cohorts also differed in terms of anemia, with NeuroAIDS PLWH reporting a higher prevalence. As the two cohorts are ethnically and culturally different, this higher prevalence can be due to these differences but also, to different rates of antiretroviral treatment. Whilst in COBRA the association between anemia and cognitive function

seems to be confounded by ethnicity, the limited number of anemic COBRA participants may have resulted in insufficient statistical power to adequately assess the role of anemia. Moreover, we cannot exclude that HIV subtype and other unmeasured socio-economic and lifestyle factors may have contributed to the different patterns of cognitive impairment observed in the two cohorts. Thirdly, the number of included Black Africans and women was relatively small, which can raise concerns about the validity of the effects observed with respect to race and sex in this study. Moreover, whilst the neuropsychological assessment was performed using a similar battery, some of the neuropsychological tests differed between the cohorts. For example, tests of language may reflect slightly different constructs such as fluency (in COBRA) and vocabulary (in NeuroAIDS). However, tests chosen here have been widely used in numerous cognitive studies and were performed using population-specific normative data to produce global T-scores.

In conclusion, although the proportion of cognitive impairment did not differ between two geographically- and ethnically-different cohorts in the current cART era, resource rich setting, risk factors and the cognitive profiles of impairment in each cohort were different. This discrepancy requires further investigations to elucidate mechanisms of HIV-associated cognitive problems in different geographical regions.

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Supplementary material

Supplementary Table 1. Review of the cognitive data from Asian populations of PLWH

Supplementary Table 2. Neuropsychological tests administered to study participants in the COBRA and NeuroAIDS studies

Supplementary Table 3. AUROC (95% CI) of individual neuropsychological tests to discriminate between individuals with and without cognitive impairment in COBRA and NeuroAIDS PLWH.