Original Article

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High prevalence of HIV-associated neurocognitive disorder in HIV-infected patients with a baseline CD4 count ≤ 350 cells/μL in Shanghai, China

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Summary **This study sought to determine the prevalence and risk factors of HIV-associated neurocognitive disorder (HAND) in HIV-infected patients with a baseline CD4 count ≤ 350 cells/μL in Shanghai, China. Subjects were 309 HIV-infected patients with a baseline CD4 count ≤ 350 cells/μL. General demographic and clinical information were collected by patient interview. Patients' cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), combined with a questionnaire on cognitive complaints. The median age of patients was 34 years (IQR: 28-43.5). In terms of sex, 272 (88.0%) of the patients were male. Of the patients, 236 (76.4%) had been on antiretroviral treatment (ART) (for a median duration of 14 months, IQR: 1-29 months) before the study. Of the patients, 183 (59.2%) mentioned having a cognitive disorder. MoCA screening revealed that the prevalence of HAND was 48.2% and that HAND was more prevalent in patients with cognitive complaints (53.0%) than in patients with no such complaints (41.3%) ($p = 0.042$). Multivariate analysis indicated that HAND was associated with being female ($p = 0.006$), being older ($p < 0.001$), having a lower level of education ($p < 0.001$), and longer use of efavirenz in an ART regimen ($p = 0.040$). This study found that HAND frequently developed in HIV-infected patients with a baseline CD4 count ≤ 350 cells/μL in Shanghai, China. Being older, being female, having a low level of education, and receiving efavirenz treatment for a longer period may be associated with a greater risk of developing HAND. This study suggests that HAND should be routinely screened for in all newly diagnosed HIV-positive patients, and especially in those with the aforementioned risk factors for developing HAND.**

Keywords: Prevalence, HIV-associated neurocognitive disorder, HIV

1. Introduction

Human immunodeficiency virus (HIV) can cause dysfunction and damage in the central nervous system (CNS), leading to a wide range of neurocognitive complications, known as HIV-associated neurocognitive disorder (HAND). Patients with HAND typically exhibit abnormalities in cognition, motor function, and behavior. Cognitive impairment predominantly consists of mental slowing, memory loss, and attention deficit. Motor symptoms include slowness and loss of balance. Behavioral changes are characterized by apathy, social withdrawal, and mood disturbances. Three forms of HAND are, in order of increasing severity, HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HIV-D) (*1*).

Highly active antiretroviral therapy (HAART) has significantly decreased the incidence of HAND (*2*). However, HIV-positive patients are living much longer than before the advent of HAART, so the prevalence

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of HAND has increased, and this is especially true for minor cognitive disorders that have a reported prevalence of 20-50% (*2,3-5*).

HAND is associated with a decrease in the quality of life, diminished compliance with HAART, and increased mortality. Therefore, an important step is to try and identify HAND, and especially in individuals with a minor cognitive disorder. Generally, HAND is assessed using a combination of neuropsychological tests, neuroimaging, and tests on the cerebrospinal fluid (CSF) that are usually expensive and time-consuming. Less expensive and less time consuming standardized symptom questionnaires (regularly administered) also play a role in clinical screening. The HIV Dementia Scale (HDS) and International HDS (IHDS) have been developed to identify HIV-D, but their usefulness at detecting milder HAND is still being studied (*6,7*). The Montreal Cognitive Assessment (MoCA) has been validated in instances of mild cognitive impairment (MCI) and is now widely used to measure cognitive functions in a variety of diseases (*8-12*). Studies have shown that the Chinese version of the MoCA has a high sensitivity and specificity at screening for MCI among the Chinese population (*13,14*).

The prevalence of and risk factors for HAND among Chinese patients have yet to be documented. This study attempted to use the MoCA to determine the frequency of HAND in a Chinese outpatient population. Risk factors associated with HAND were also assessed, potentially providing useful clinical indicators.

2. Materials and Methods

2.1. *Selection of study subjects*

A cross-sectional survey of HIV-1 positive patients treated in the outpatient facility of the Shanghai Public Health Clinical Center (Shanghai, China) was conducted from May 2012 to February 2013. Potential subjects were 309 patients who had their cognitive function tested. Inclusion criterion were a recent diagnosis with HIV-1 infection or already being on HAART, age ≥ 18 years, and having a baseline $CD4^+$ T cell count ≤ 350 cells/μL. Exclusion criteria were: age < 18 years, suffering a major opportunistic infection of the brain in the past 3 years, psychoactive drug use, alcohol addiction, physical disability (*e.g.* amputation), major depression, having a severe systemic disease that might affect testing, and being pregnant. Of the potential subjects, 118 declined to participate in the study either because they thought the tests were troublesome and time consuming or because they did not think that they had neurocognitive problems.

2.2. *Data collection*

General demographic and clinical information, including sex, age, educational level, medical history, and previous HAART (when HAART was started and the details of the HAART regimen), were collected by patient interview.

Cognitive function assessment: The tests below were used to assess the cognitive function of all of the patients studied.

Cognitive complaints questionnaire: A short questionnaire asked four questions to screen for cognitive complaints: "Do you experience frequent memory loss (*e.g.* do you forget the occurrence of certain events, like appointments, and especially more recent ones)," "Do you feel that you are slower when reasoning, planning activities, or solving problems," "Have you lost interest in previous activities and hobbies," and "Do you have difficulty managing your daily affairs." For each question, answers were "never," "hardly ever," or "yes, definitely." Patients answering "yes, definitely" to at least one question were deemed to have cognitive complaints.

The Chinese version of the MoCA: The MoCA (*http://www.mocatest.org*) assesses several cognitive domains. The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visualspatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the trail-making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points). The MoCA has a total score of 30 points, and < 26 points is the cutoff point for cognitive impairment. An adjustment was made for educational level by adding one point to the final score if the patient was educated for less than 12 years.

2.3. *Statistical methods*

Data were analyzed using Stata v. 10.0. Continuous data with a normal distribution were expressed as means ± standard deviation (mean ± S.D.) and compared using *t*-tests; continuous data with a skewed distribution were expressed as medians (inter-quartile range, IQR) and compared using the Wilcoxon rank sum test. Categorical data were expressed in frequencies and percentages and compared using chi-square (χ^2) tests, with a $p < 0.05$ considered to be statistically significant.

3. Results

3.1. *General information of the patients studied*

Subjects for this study were 309 patients who had their neurocognitive function tested. Of these, 272 (88.0%) were male and 37 (12.0%) were female. The median age was 34 years (IQR: 28-43.5), and 236 (76.4%) patients had undergone antiretroviral treatment (ART) for a median duration of 14 months (IQR: 1-29). The ART regimens were: zidovudine or stavudine or tenofovir + lamivudine + efavirenz or nevirapine or lopinavir/r. There were no statistically significant differences in median age, age distribution, number of patients on ART, and ART duration between male and female patients ($p = 0.87$, $p = 0.28$, $p = 0.92$, $p = 0.05$). However, male patients had a significantly higher educational level compared to female patients ($p < 0.01$) (Table 1).

3.2. *Prevalence of cognitive complaints in the patients studied*

Based on the devised questionnaire, the prevalence of cognitive complaints among HIV-1 positive patients was 59.2% (183/309): 38.8% (120/309) had memory difficulties, 34.3% (106/309) had mental slowing, 24.6% (76/309) had difficulty managing daily affairs, and 10.4% (32/309) had lost interest in previous activities and hobbies. In terms of the number of complaints, 89 patients had only one complaint, 54 patients had 2 complaints, 23 had three complaints, and 17 had four complaints.

3.3. *Prevalence of HAND in the patients studied and comparison of HIV-1 positive patients with and without HAND*

Overall, 160 patients (51.8%) had normal MoCA scores (≥ 26) and 149 patients (48.2%) had abnormal MoCA scores (< 26). The prevalence of HAND was 48.2% (149/309) in HIV-1 positive patients overall, 53.0% (97/183) in patients with a cognitive complaint, and 41.3% (52/126) in patients without a cognitive complaint. HAND was more prevalent in patients with cognitive complaints than in patients with no such complaints ($\chi^2 = 4.116$, $p = 0.042$). Compared to patients without HAND ($n = 160$), patients with HAND ($n = 149$) were more likely to be women ($p = 0.004$), of older age ($p < 0.001$), less educated ($p < 0.001$), had undergone ART for a longer period ($p = 0.006$), and had been treated with efavirenz (EFV) for longer ($p = 0.019$). No significant differences were observed in MoCA scores based on ART initiation ($p = 0.960$) and central nervous system (CNS) penetration-effectiveness (CPE) of HAART ($p = 0.830$) (*15*). Cognitive complaints were more prevalent in patients with HAND, but the difference was not statistically significant ($p = 0.117$). However, a larger proportion of patients with HAND had ≥ 3 complaints compared to patients without HAND ($p = 0.003$) (Table 2).

3.4. *Multivariate analysis of the MoCA score*

The results of multivariate analysis are shown in Table 3. These results indicate that HAND was associated with sex ($\beta = -1.052$, $p = 0.006$, OR = 0.35), age ($\beta = -0.109$, $p < 0.001$) , level of education < 12 years ($\beta = -1.415$, $p < 0.001$, OR = 4.12), and duration of ART ($\beta = -0.020$, $p = 0.040$). Since the side effects of EFV on CNS may influence the MoCA score, the correlation between duration of treatment with EFV and HAND was analyzed, and no association between the total duration of treatment with EFV and HAND was noted ($\beta = -0.026$, $p = 0.060$). However, patients treated with EFV ≥ 24 months had a greater risk of developing HAND ($\beta = -0.745$, $p = 0.020$, OR = 2.11). Being female and having a lower level of education were also possible risk factors for developing HAND. An older age and longer duration of ART were positively correlated with development of HAND.

Table 1. Clinical and demographic information on the patients studied

Items	Male ($n = 272$)	Female ($n = 37$)	Total ($n = 309$)	Statistic	p-value
Age (years)*	34 (28.3-43)	33 (28-48.5)	34 (28-43.5)	$Z = 0.163$[a]	0.87
< 30	78 (28.7%)	13 (35.1%)	91(29.5%)	$\chi^2 = 5.06$[b]	0.28
30-40	104 (38.2%)	10 (27.0%)	114 (36.9%)		
40-50	54 (19.9%)	5 (13.5%)	59 (19.1%)		
50-60	29 (10.6%)	7 (18.9%)	36 (11.7%)		
> 60	7 (2.6%)	2 (5.4%)	9 (2.9%)		
Educational level (years)					
≤ 12	86 (31.6%)	24 (64.9%)	110 (35.6%)	$\chi^2 = 15.703$[c]	< 0.01
On ART	208 (76.5%)	28 (75.7%)	236 (76.4%)	$\chi^2 = 0.011$[c]	0.92
ART duration (months)*	12 (1-27.8)	24 (4-37.5)	14 (1-29)	$Z = -1.991$[a]	0.05

*, Data are presented as the median (IQR); ART, antiretroviral therapy; [a], Wilcoxon rank sum test; [b], CMH chi-square test; [c], chi-square test.

Table 2. Comparison of patients with HAND and patients without HAND

Items	Without HAND (n = 160)	With HAND (n = 149)	Statistic	p-value
Sex				
Male	149 (54.8%)	123 (45.2%)	$\chi^2 = 8.185^a$	0.004
Female	11 (29.73%)	26 (70.27%)		
Age (years)*	31.5 (27-36)	40 (31-49)	$Z = -5.870^b$	< 0.001
< 30	61 (67.0%)	30 (33.0%)	$\chi^2 = 39.95^c$	< 0.001
30-40	71 (62.3%)	43 (37.7%)		
40-50	18 (30.5%)	41 (69.5%)		
50-60	8 (22.2%)	28 (77.8%)		
> 60	2 (22.2%)	7 (77.8%)		
Educational level (years)				
≤ 12	33 (30.0%)	77 (70.0%)	$\chi^2 = 32.451^a$	< 0.001
> 12	127 (63.8%)	72 (36.2%)		
ART initiation				
Yes	122 (51.7%)	114 (48.3%)	$\chi^2 = 0.003^a$	0.960
No	38 (52.1%)	35 (47.9%)		
Duration of ART (months)*	10 (0.8-22.8)	17 (1-36.5)	$Z = -2.755^b$	0.006
ART regimen including EFV				
Yes	90 (56.3%)	80 (53.7%)	$\chi^2 = 0.204^a$	0.651
No	70 (43.7%)	69 (46.3%)		
Duration of treatment with EFV (months)(n = 170)				
≤24	62 (60.2%)	41(39.8%)	$\chi^2 = 5.518^a$	0.019
> 24	28 (41.8%)	39 (58.2%)		
CPE score of HAART*	9 (7-9)	9 (7-9)	$Z = 0.214^b$	0.830
Cognitive complaints (n = 183)	88 (55.0%)	95 (63.8%)	$\chi^2 = 2.451^a$	0.117
≤ 2	78 (48.8%)	67 (45.0%)	$\chi^2 = 9.106^a$	0.003
≥ 3	10 (6.3%)	28 (18.8%)		

*, Data are presented as the median (IQR); EFV, efavirenz; ART, antiretroviral therapy; [a], chi-square test; [b], Wilcoxon rank sum test; [c], CMH chi-square test; CPE, central nervous system penetration-effectiveness rank, the CPE score was calculated by adding up the scores of each antiretroviral drug in the regimen (tenofovir = 1, lamivudine and stavudine = 2, efavirenz and lopinavir/r = 3, and zidovudine and nevirapine = 4).

Table 3. Results of multivariate analysis of the MoCA score

Items	β	p-value	OR	95% CI
Sex (female)*	-1.052	0.006	0.35	0.17-0.74
Age#	-0.109	< 0.001	/	/
Educational level < 12 years*	-1.415	< 0.001	4.12	2.5-6.79
Duration of ART#	-0.020	0.040	/	/
Duration of treatment with EFV#	-0.026	0.060	/	/
Duration of treatment with EFV ≥ 24 months*	-0.745	0.020	2.11	1.13-3.94

*, Logistic regression analysis; #, Linear regression; EFV, efavirenz; ART, antiretroviral therapy.

4. Discussion

Results indicated that 59.2% of HIV-1 positive patients with a baseline CD4 count ≤ 350 cells/μL complained of neurocognitive symptoms, including memory difficulties, mental slowing, difficulty managing daily affairs, and losing interest in activities one "used to do." Screening *via* the MoCA score revealed that 48.2% of the patients overall presented with HAND, with a higher prevalence among patients with neurocognitive complaints (53.0%) than among patients with no such complaints (41.3%). This finding shows that there is a high prevalence of cognitive impairment even in HIV-1 patients without any neurocognitive complaints. Thus, the potential for patients with no cognitive complaints to develop HAND should be kept in mind. The median age of subjects in this study was only 34 years of age, suggesting that HAND may be the predominant cause of cognitive dysfunction/dementia among young people. The prevalence of HAND in this study is similar to that in previous studies (*2,4,5*). This prevalence is lower than that in the study by Simioni *et al*. (*16*), possibly because of the differences in the screening methods used and the study samples. In addition, 118 eligible

patients declined to participate in the cognitive testing in the current study, and this inclusion bias might have affected the results.

Results of the current study indicate that being older, being female, having a lower level of education, a longer duration of HAART, and use of EFV ≥ 24 months in HAART regimens may contribute to an increased risk of developing HAND. In other studies, HAND is also reported to be more prevalent in patients who were older and who had lower levels of education (*17,18*). However, MoCA was not used to assess neurocognitive disorders in non-HIV infected controls matched by age and educational level in the current study. Thus, whether such HIV-independent changes potentially affect MoCA scores is unclear and requires further study. In contrast to the current results, a study by Joska *et al*. showed that being male rather than female was predictive of development of HIV-associated dementia (*18*). The disparity in findings can perhaps be explained by the fact that the female patients in the current study were significantly less educated than male patients. Surprisingly, a longer duration of HAART was found to be associated with a higher prevalence of HAND. HAART does not apparently prevent the development of HAND nor successfully treat HAND. This contradicts a recent study that noted a decrease in HAND proportional to the duration of HAART (*19*). However, the current results should not be taken to mean that HAART is not an effective treatment for HAND since most of the patients studied (72%, 170/236) were already on HAART before the study began and they were administered ART including EFV, which has side effects on the CNS including dizziness, impaired concentration, somnolence, abnormal dreams, and insomnia. These symptoms may result in patients having a poorer cognitive performance. This hypothesis is supported by a recent study reporting that efavirenz is associated with cognitive disorders in otherwise asymptomatic HIV-infected patients (*20*). Other previously reported risk factors for HAND include a decreased CD4 count, anemia, declining platelet count, high HIV-RNA viral load in the CNS, and hepatitis C coinfection (*20-22*).

The pathogenesis of HAND is not yet clear. A tentative hypothesis is that HIV-1 itself can cause dysfunction and damage in the CNS. Shortly after the primary infection, HIV-1 enters the brain in mononuclear cells and settles in perivascular macrophages and microglial cells. Replication of HIV-1 in these cells leads to immune activation and the production of viral and inflammatory proteins, which may be what eventually leads to various cognitive disorders. Studies have shown that antiretroviral drugs with a higher CPE are associated with a lower HIV-RNA load in CSF and better cognitive performance (*15,19*). The current study noted no significant differences in CPE in patients with normal or abnormal MoCA scores. This may be because there are limited anti-HIV drugs in China and HAART regimens for most patients consisted of the same drugs. In addition, HAND is not routinely screened for prior to commencing ART in order to give drugs with higher CPE scores to patients with HAND.

Having been validated in instances of mild cognitive impairment, MoCA could perhaps be used to screen for HAND, in combination with a neurocognitive complaint questionnaire, as was done in this study. Further study is needed to assess the ability of MoCA versus other methods of cognitive assessment to assess HIV-associated cognitive impairment. Combining MoCA with other cognitive and functional assessments may allow more accurate diagnosis of HIV-related cognitive impairments.

In conclusion, the current results show that neurocognitive disorders are frequent in HIV-infected patients with a baseline CD4 count ≤ 350 cells/μL in Shanghai, China. Being older, being female, having a low level of education, and a longer period of EFV use in HAART regimens may be associated with a greater risk of developing HAND. These data suggest that HAND needs to be screened for regularly in all newly diagnosed HIV patients, and perhaps in all patients on a routine schedule (especially in those patients with risk factors for HAND), in order to diagnose HAND and possibly intervene as early as possible.

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