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Evaluation of Three Brief Screening Tests for Older Patients with Mild HIV-Associated Neurocognitive Disorders in the cART Era

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Abstract

Introduction: Prevalence of HIV-associated neurocognitive disorders (HAND) in the era of antiretrovirals is still high, the majority of clinical phenotypes being represented by mild forms of impairment. Therefore, adequate screening strategies are needed.

We compared performance of three brief screening tools for detecting mild forms of HAND in an elderly population.

Methods: Randomly selected patient over 50 years performed a complete neuropsychological evaluation, considered as the gold standard and three brief screening tools: International HIV Dementia Scale (IHDS), Montreal cognitive assessment (MOCA) and a French battery named FIMF and composed by: Frontal ability battery, Isaac set test, Memory span test and Five words test. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of screening tools and possible combinations were analyzed.

Results: 49 patients were tested (mean age 57, 78% men, nadir CD4 252, CD4 cell count at inclusion 616, 86% with viral load below 50 copies/ml, 18% HCV co-infected, 18% previous illicit drug use, 16% with AIDS). HAND was diagnosed in 30/49 patients (90% asymptomatic neurocognitive disorder, 10% mild neurocognitive disorder).

In detecting HAND, the FIMF battery showed the best performances (sensitivity 87%, specificity 47%, PPV 72%, NPV 69%). Combination of MOCA, Isaac set test and Memory span test showed sensitivity 90%, specificity 47%, PPV 73%, NPV 75%, with a combined cut-off value of 78 for discriminating HAND.

Conclusion: The combination of MOCA, Isaac set test and Memory span test showed better performances than the majority of screening tools available for detecting mild forms of HAND and should therefore be considered as a useful option for identifying patients requiring neuropsychological evaluation.

Keywords: HIV-associated neurocognitive disorders; Screening tools; cART era

Introduction

In the era of combination antiretroviral therapies (cART), prevalence of HIV-associated neurocognitive disorders (HAND) is still high, especially in patients over 50 years old, probably as a consequence of age-related cognitive decline and the increasing number of comorbid conditions [1-6]. Indeed, Valcour et al. showed that patients older than 50 years have three-fold higher risks for HIV-associated dementia than younger subjects [3].

The clinical phenotype of neurocognitive disorders in the cART era is generally represented by asymptomatic neurocognitive impairment (ANI) and mild neurocognitive impairment (MND) (90% of HAND diagnosis), while cases of HIV-associated dementia are very rare [7,8].

These less severe forms of HAND, however, are associated with loss of quality of life, poorer treatment compliance and in general higher mortality [9,10]. Therefore, one of major challenges in the cART era is to diagnose these forms of impairment in order to prevent such complications.

While the gold standard for assessing diagnosis of HAND is a detailed battery of neuropsychological tests [11], which lasts approximately 1 h and half, the availability of neuropsychologists is scarce in some hospital settings. Therefore, several easy-to-perform screening tools have been developed for identifying patients needing more detailed evaluation [12-15], but their performance for detecting mild forms of HAND has been variable.

In particular, a number of screening tools have been specifically introduced for patients with HIV-associated dementia (HAD), such as the HIV Dementia scale and the International HIV Dementia scale (IHDS) [16,17]. Other tools, such as the Mini mental state examination (MMSE) and the Montreal cognitive assessment (MOCA) have been

used for the HIV population, often with scarce performance in non-demented patients [18-21].

Therefore, more performing tools for detecting patients at risks for mild forms of HAND are needed. A novel screener, named Cognitive Assessment Tool-rapid version (CAT-rapid), combined with IHDS, showed excellent sensitivity and specificity for patients with HAD, while it failed to identify patients with mild HAND [22].

We conducted a prospective study using three different screening tools in a population of HIV-infected patients older than 50 years, where prevalence of HAND is particularly high and the phenotype of impairment is mainly represented by ANI and MND.

Methods

Participant's selection

We randomly selected HIV-1-infected patients above 50 years of age among patients followed in the Department of Internal Medicine at Cannes General Hospital. No limits were set concerning CD4+ cell count or HIV viral load.

Exclusion criteria included active opportunistic infection, a change in psychotropic therapy within the past 3 weeks or any neurological history. Patients were asked to provide informed consent. The study was approved by the Ethics Committee.

Neuropsychological evaluation

Each patient performed a wide range of neuropsychological (NP) tests administered by a single trained neuropsychologist.

According to the American Academy of Neurology (AAN) 2007 revised criteria [11], tests explored a wide spectrum of cognitive domains: learning and recall episodic memory, attention/concentration, working memory, executive functions, language, visual agnosia and motor/psychomotor speed. Duration of NP evaluation was 2 h.

The following tests were used:

- Mini Mental State Evaluation (MMSE) for evaluation of global cognitive function [23]

- Grober and Buschke test (also called RL/ RI 16 according to French guidelines) for episodic memory (learning and recall) [24]

- Stroop test for attention/concentration and speed of information processing [25]

- Verbal Fluency for executive functions and lexical access ability [26]

- « Protocole Montreal-Toulouse d'Evaluation des Gnosies Visuelles » for visual agnosia [27]

- Digit Span and Letter-Number-Sequencing for attention/concentration and working memory [28]

- Grooved Pegboard for motor and psychomotor speed abilities [29]

- Matrix Reasoning and The Trail Making Test for executive functioning [30]

- « Test de Denomination Orale d'Image » for language [31]

- The Mahieux Brief Screening Scale for praxic abilities [32]

The NP scores from each test were transformed into z-scores as described elsewhere [33] and were adjusted for age, gender and years of education, using standardised norms.

Patients were also assessed according to the Montgomery and Asberg Depression Rating Scale (MADRS) to elicit potential behavioural disorders. Moreover, in order to evaluate the potential interference of HAND on daily functioning, patients also performed the Instrumental Activity of Daily Living short version battery, the Mac Nair and Khan questionnaire of cognitive complaints, the Multiple sclerosis Neurological questionnaire and the Perceived Deficits questionnaire.

According to the AAN revised criteria [11], patients with HAND at NP testing were subdivided into 3 categories:

ANI, involving at least two cognitive domains and documented by a performance of at least 1 SD below the mean on NP tests, without interference in everyday functioning. The asymptomatic characteristics of impairment were defined by the Instrumental Activity of Daily Living short version battery and by interviewing the patient and his/her family.

MND, involving at least two cognitive domains and documented by a performance of at least 1 SD below the mean on NP tests, with mild interference in daily functioning.

HAD, involving at least two cognitive domains and documented by a performance of 2 SD below the normative mean on NP tests, with marked interference in daily functioning

Thus, each patient performing 1 SD or more below the mean in at least two cognitive domains was considered as presenting with HAND and classified as ANI or MND, according to interference with daily living, while those performing 2 SD or more in at least two cognitive domains were classified as HAD.

Screening Tools

In addition to this large battery of neuropsychological tests, which was considered as the gold standard, we proposed to each patient three screening tools, within 3 months from the date of the large battery. The order among the three screening tools was systematically changed, in order to avoid potential bias linked to patient's learning.

The three screening tools used in this study were:

IHDS: it includes measures of psychomotor speed and processing, as well as short-term memory. It scores a maximum of 12 points and in case of performances below 11 patient requires further evaluations [16]

MOCA: it measures attention/concentration, language, episodic memory and executive function, while it does not measure psycho-motor speed or speed of information processing. It scores a maximum of 30 points and results below 26 are considered as pathological. In case of education level below high school, 1 point is added to the final score [34]

A local battery, suggested by French national guidelines for the management of HAND [35] and named FIMF as abbreviation of 4 sub-tests initials included:

The frontal ability battery (FAB): It allows a rapid evaluation of executive functions. FAB has the validity for discriminating between fronto-temporal type dementia and Alzheimer disease in mildly demented patients (MMSE>24). It includes the following items:

similarities, lexical fluency, motor series "Luria" test, conflicting instructions, inhibitory control and prehension behaviour. Each item has a maximum score of 3. A total cut-off score of 16 is considered as pathological for patients with high school education level or higher, while the cut-off is 15 for those with lower education level [36].

Isaac set test: It is a test on verbal fluency, where patients are asked to cite the highest number of words they can in 4 semantics categories (colours, animals, fruits and cities). For each category, performances are measured on 15 seconds and the operator stops when 10 words are cited or patient has no more word to cite. A global cut-off below 38 is considered as pathological [37].

Memory span test: Commonly used in the Weschler Adult intelligence Scale (WAIS), it measures skills in working memory. The operator presents an increasing series of numbers and patient has to repeat them few moments later and, in a second phase, reversing their order. Subjects not able to correctly reproduce a series of minimum 5 numbers are considered as pathological and need further evaluations [38].

The five words test (FWT): It is a simple and rapid item initially introduced for testing patients with Alzheimer disease. It consists in showing a list of five words to the patient (usually Museum, Lemonade, Grasshopper, Colander and Truck). In accordance with Grober and Buschke neuropsychological concept, it allows assessment of verbal episodic memory [39]. The main steps of the FWT consist of: inducing specific semantic processing, controlling encoding in order to avoid attention deficits and measuring free and cued recall. Cued recall helps to distinguish recall impairment from storage impairment which is evocative of Alzheimer disease. The maximum score is 10 and each performance below this cut-off is considered as pathological [40].

Statistical Analysis

Associations between NP testing results (Group without HAND vs Group with HAND) and potential risk factors were studied in univariate analyses using the χ^2 test for categorical variables and Mann-Whitney test for continuous ones. P-values below 0.05 were considered statistically significant. Statistical analyses were performed using SPSS® software.

According to correspondent cut-off values, we then coded each test of the screening tools as normal or impaired. Considering the NP large battery as the gold standard, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were measured for the screening tools (IHDS, MOCA and FIMF). Concerning the FIMF battery, we firstly measured performances of each sub-test, than the entire battery, considering as impaired subjects with at least one of four sub-tests below the norms.

Once most performing tests were identified, we then tried to look at combinations of tests from different screening tools in order to define the best set.

In addition to this analysis where screening tools were considered as a qualitative variable (normal or impaired), we analysed performances in the combination of tests as a quantitative variable, according to scores for each test, in order to identify a global cut-off value which could be discriminant for HAND. A receiver operating characteristic (ROC) curve was then created for this analysis.

Results

Characteristics of patients

From September 2012 to October 2013, 49 subjects have been randomly included (mean age 57, 78% men, nadir CD4 252, CD4 cell count at inclusion 616, 86% with viral load below 50 copies/ml, 18% HCV co-infected, 18% previous IDU, 16% with AIDS. Among co-morbid conditions, 36% had hypertension, 33% dyslipidemia, 33% smoking and 18% HCV co-infection, Table 1).

NP testing results

According to the NP large battery, 30 out of 49 patients had HAND (61%), with the large majority represented by ANI (27 out of 30, 90%), while 3 had MND (10%) and anyone HAD.

Main impairments found were executive functions (20 out of 30 patients, 67%), working memory (19/30, 63%), motor speed (13/30, 43%), speed of information processing (12/30, 40%) and learning memory (12/30, 40%). No patients were suffering from severe depression.

Characteristics of patients did not differ between the HAND and no HAND group, apart from more smokers among impaired subjects (Table 1).

	Total population	Patients without HAND	Patients with HAND	p value
	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	
Number of patients	49	19	30	
Male	38 (78)	13 (68)	25 (83)	0.23
Age (years)	56,8 (4,6)	57 (4,8)	57 (4,6	0.99
Education level below high school	34 (69)	12 (63)	22 (73)	0.45
Previous IDU	9 (18)	3 (16)	6 (20)	0.71
Duration of HIV infection (years)	17,6 (8,3)	17 (9)	17,9 (7,9)	0.7
Previous AIDS event	8 (16)	3 (16)	5 (17)	0.93
Hepatitis C co-infection	9 (18)	2 (11)	7 (23)	0.24

Hypertension	17 (35)	6 (32)	11 (37)	0.71
Dyslipidemia	16 (33)	8 (42)	8 (27)	0.26
Smoking	16 (33)	3 (16)	13 (43)	0.03
History of cancer	34 (69)	12 (63)	22 (73)	0.45
Patients with HIV-RNA <50 copies/ml	42 (86)	15 (79)	27 (90)	0.29
Mean CD4 cell count (cells/mm^3)	616 (246)	649 (205)	595 (269)	0.45
Mean CD4 nadir (cells/mm^3)	252 (195)	251 (154)	253 (218)	0.97

Table 1: Characteristics of patients at inclusion.

Screening tools results

Comparison between IHDS, MOCA and FIMF batteries showed the best performances for the latter. In particular, sensitivity, PPV and NPV for the FIMF battery were 87%, 72% and 69%, respectively, while specificity was 47% (Table 2).

As the Five words test and Frontal ability battery did not allow good performance at all, we eliminated them from the screening tool and tried to look at other combinations of tests. The best results were obtained when combining Isaac set test, Memory span test and MOCA, allowing high values of sensitivity, PPV and NPV when performances were below the cut-off for at least one of them (Table 2).

Screening tool (cut-off)	No HAND (n=19)		HAND (n=30)		Sensitivity (%)	Specificity (%)	VPP (%)	VPN (%)
	n	%	n	%				
IHDS (≤ 10)					70.0	47.4	67.7	50.0
No	9	50.0	9	50.0				
Yes	10	32.3	21	67.7				
MOCA (<26)					36.7	84.2	78.6	45.7
No	16	45.7	19	54.3				
Yes	3	21.4	11	78.6				
Five words test (<10)					6.7	89.5	50.0	37.8
No	17	37.8	28	62.2				
Yes	2	50.0	2	50.0				
Frontal ability battery (≤ 15)					13.3	94.7	80.0	40.9
No	18	40.9	26	59.1				
Yes	1	20.0	4	80.0				
ISAAC set test (≤ 38)					76.7	63.2	76.7	63.2
No	12	63.2	7	36.8				
Yes	7	23.3	23	76.7				
Memory span test (<5)					30.0	78.9	69.2	41.7
No	15	41.7	21	58.3				
Yes	4	30.8	9	69.2				
French battery: Five words test (<10) or Frontal ability battery (≤ 15) or Isaac set test (≤ 38) or Memory span test (<5)					86.7	47.4	72.2	69.2
No	9	69.2	4	30.8				

	n	%	n	%	Sensitivity	Specificity	PPV	NPV
Yes			10	27.8	26	72.2		
Isaac set test (≤ 38) or Memory span test (<5) or MOCA (<26)					90.0	47.4	73.0	75.0
Non	9	75.0	3	25.0				
Yes	10	27.0	27	73.0				
Isaac set test (≤ 38) and Memory span test (<5) and MOCA (<26)					10.0	94.7	75.0	40.0
Non	18	40.0	27	60.0				
Yes	1	25.0	3	75.0				

Table 2: Performance of screening tools.

	No HAND (n=19)		HAND (n=30)					
	n	%	n	%	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MOCA+Isaac set test+Memory span test (≤ 76)					63.3	57.9	70.4	50.0
No	11	50.0	11	50.0				
Yes	8	29.6	19					
MOCA+Isaac set test+Memory span test (≤ 77)					66.7	52.6	69.0	50.0
No	10	50.0	10	50.0				
Yes	9	31.0	20	69.0				
MOCA+Isaac set test+Memory span test (≤ 78)					80.0	52.6	72.7	62.5
No	10	62.5	6	37.5				
Yes	9	27.3	24	72.7				
MOCA+Isaac set test+Memory span test (≤ 79)					80.0	31.6	64.9	50.0
No	6	50.0	6	50.0				
Yes	13	35.1	24	64.9				
MOCA+Isaac set test+Memory span test (≤ 80)					83.3	31.6	65.8	54.5
No	6	54.5	5	45.5				
Yes	13	34.2	25	65.8				

Table 3: Combination of tests and cut-off values (Area under the ROC curve: 0,635).

Using Roc curves, the cut-off value of 78 for the combination of these three tests showed the best performances (Table 3 and Figure 1).

Discussion

In a population of older HIV-infected patients, a high percentage of subjects were diagnosed with mild forms of HAND, the majority of impairment represented by a sub-cortical phenotype, such in younger individuals, but also, in some cases, by learning deficit. These results confirm what has been previously showed in cART experienced elderly HIV-infected subjects, where a mixed cortical-subcortical phenotype of impairment could be detected [9,41,42]. No cases of severe depression were found, thus reducing risks for confounding behavioural disorders.

We compared three different screening tools. Performances of IHDS and MOCA were poor, confirming their limits for detecting HAND in the cART era, where most frequent phenotypes are represented by mild impairments, symptomatic or not.

The FIMF battery showed the best performances, although specificity was poor. The combination of two tests included in this battery (Isaac set test and Memory span test) with MOCA displayed still more interesting results. Although poor specificity requires further more performing tools, these results are encouraging considering that the large majority of impaired patients had the mildest and most difficult to diagnose form of HAND, represented by ANI. A cut-off value of 78 for this combination of tests had been identified for discriminating patients with HAND, but the best performances seem to be joined when considering subjects as impaired simply in case of at least one test below the norms.

Figure 1: Receiver operating characteristic (ROC) curve combining MOCA, Isaac set test and Memory span test. Unimpaired subjects versus patients with HAND (Area under the curve=0.635).
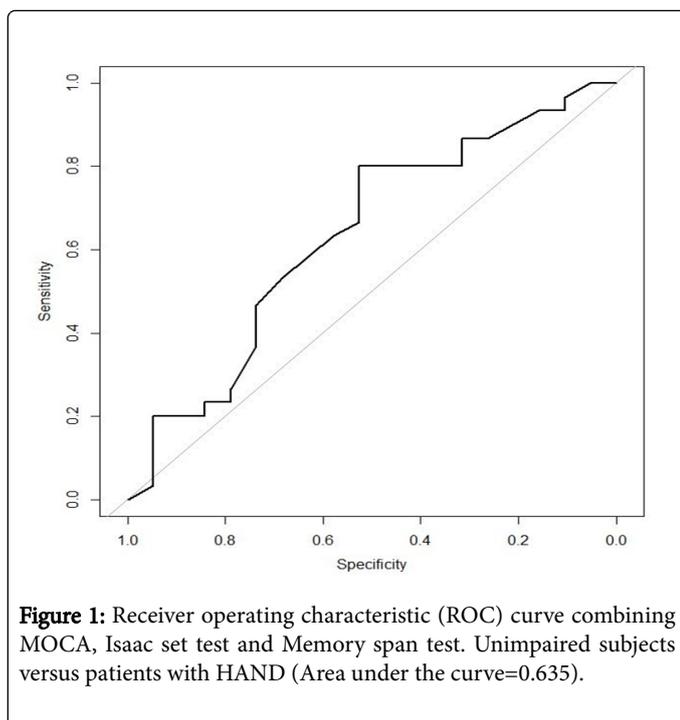
ANI is the most frequent form of HAND in the cART era. Its role is controversial, as some authors had suggested potential risks of over-diagnosis due to too severe norms of the AAN revised criteria [43,44]. Moreover, we recently showed that aviremic patients with ANI do not display the same pattern of immune activation than MND, suggesting that this definition is not stringent and not represent overt disease, or that it is a pre-clinical condition of more severe forms of impairment [34]. However, others have showed that patients with ANI have higher risks to deteriorate over time than unimpaired subjects [45-47]. Therefore, despite the ongoing debates about its real role, diagnosing ANI is one of main priorities and difficulties in the management of HAND in the cART era. Screening tools could be useful for identifying patients needing more accurate NP evaluation in order to confirm diagnosis, especially in settings where availability of neuropsychologists for the clinical routine is scarce.

Our results, although they are more favourable than other screening batteries currently used for detecting HAND, show poorer performances than the recently published CogState-based screening procedure [13]. Indeed, Bloch et al. found excellent results in terms of sensitivity, specificity, PPV and NPV in a population of HIV-infected patients mainly presenting with mild forms of HAND. However, this study is hampered by some methodological bias that limits its definitive validation as the gold standard among screening tools. Indeed, authors did not test the entire population with the large NP battery, but only those having the poorest performances with the CogState screening test, while subjects with ANI or normal tests were not systematically tested by the large battery. This method limits, to us, the real capacity of such screening battery to detect the mildest forms of HAND and risks to overestimate its performances by potentially excluding patients with false normal performances with the screening battery. Moreover, a significant number of subjects included had potential confounding factors such as previous CNS opportunistic infections or a history of non-HIV neurological or psychiatric condition.

Among limits of our study, there are the small number of subjects included, the lack of a control group of HIV-subjects and the absence of a screening test for speed of information processing, which probably would have improved performances of such tools. Indeed, screening tools usually focus only on some neurocognitive domains in order to obtain some easy-to-perform tools, thus potentially limiting their performances. Besides, although difference was not statistically significant, there was an overrepresentation of women in the HAND group compared to the majority of men in the entire population studied. Moreover, although the large majority of subjects included were Caucasians, where clade B viruses are the most prevalent, we did not include in the analysis data about subtypes of HIV, which could potentially alter performances on NP testing. Another limit of the study could be the low number of subjects detected with MND, which is in line with the majority of studies on prevalence of HAND in the cART era. Indeed, the large majority of phenotypes of impairment are at present represented by the ANI group. Therefore, although both ANI and MND reflect mild neurocognitive disorders according to the AAN revised criteria, these subgroups were not equally represented, as a consequence of the study design.

Conclusion

In conclusion, the combination of MOCA, Isaac set test and Memory span test could be considered as a useful easy-to perform screening tool for identifying mild forms of HAND in the cART era.

Author's Contributions

Conceived and designed the study: MV. Performed the study: MV, LB. Analysed data: RB, CP. Wrote the manuscript: MV, BD. Edited the manuscript: SA, NM, CLF, HJ.

Conflict of Interest

The authors have no conflict of interest to declare.

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