Is International HIV Dementia Scale good enough to diagnose HIV-associated neurocognitive disorders?

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ABSTRACT

Introduction: Human immunodeficiency virus (HIV)-associated neurocognitive disorders (HAND) comprise impairment of multiple cognitive domains and cause significant morbidity. International HIV Dementia Scale (IHDS) is a quite sensitive and specific method for screening for HAND, and Modified Mini-Mental State Examination (3MS), though nonspecific, contains more parameters for screening for neurocognition. Hence, we compared 3MS and IHDS as screening tools for HAND with an aim to find out which was a better screening tool for HAND. **Methods:** Using 3MS and IHDS, we assessed the cognitive status of 200 HIV-positive patients (65% males) and 84 controls, presenting to the Department of Medicine, King George's Medical University, Lucknow, India from September 2015 to September 2019. **Results:** According to 3MS, 42 (21%) HIV-positive patients were neurocognitively impaired (mean 76.24 ± 1.51), and 158 (79%) patients were not (mean 87.02 ± 4.16). As per IHDS, 185 (92.5%) HIV patients were neurocognitively impaired (mean 8.45 ± 0.88), and 15 (7.5%) patients were not (mean 11.13 ± 0.35). The mean 3MS score of controls was 87.56 ± 4.26, and the IHDS score was 9.73 ± 1.00. According to Patient Health Questionnaire-9 (PHQ-9), moderate depression occurred in only 3.5% of the patients, and the rest had only minimal or mild depression. In IHDS, psychomotor speed was the most affected parameter, whereas in 3MS, similarities were the most affected. **Conclusion:** IHDS may be over diagnosing neurocognitive impairment in HIV patients due to difficulty in understanding the test, especially psychomotor speed testing. 3MS may be more accurate for detecting neurocognitive impairment in HIV patients, and scale combining both these methods may be a still better choice.

Keywords: 3MS, AIDS, dementia, HAND, HIV, IHDS, neurocognition

Introduction

Human immunodeficiency virus (HIV)-associated disease is a major cause of morbidity and mortality worldwide. In 2015, there were approximately 36.7 million people living with HIV/ acquired immunodeficiency syndrome (AIDS), according to a United Nations Programme on HIV and AIDS (UNAIDS) estimate,[1] India has the third-highest number of people living with HIV disease (PLWHIV) in the world though the number has been declining since 2007 with numbers coming down from 2.23 million to 2.12 million in 2015.[2,3]

HIV-associated neurocognitive disorders (HAND) comprise impairment of multiple cognitive domains in patients suffering from HIV disease, in the absence of other causes for the impairment.[4] HIV infection most prominently affects the domains of motor functioning, attention, processing speed, executive functioning, and memory.[5,6]

Access this article online

Quick Response Code:

Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_356_21

How to cite this article: Himanshu D, Tandon R, Kumar S, Sawlani KK, Verma SK, Misra R, *et al*. Is International HIV Dementia Scale good enough to diagnose HIV-associated neurocognitive disorders? J Family Med Prim Care 2022;11:5060-4.

HAND is quite prevalent worldwide with prevalence in different studies varying between 5% and 85%, and as such, is a significant cause of morbidity. The prevalence of severe forms of HAND has been decreasing in recent times due to the early initiation of antiretroviral therapy (ART), but less severe forms of HAND still remain.[7-10]

There are various methods of assessing neurocognition clinically, which include Mini-Mental Scoring (2MS), Modified Mini-Mental Scoring (3MS), and International HIV Dementia Scoring (IHDS). Out of these, most of the previous studies have used 2MS and IHDS for assessing the cognitive dysfunction in these patients. Researchers consider IHDS to be more sensitive (62%–80%) and specific (55%–80%) than others in picking up cognitive changes in these patients.[8,10-14]

Among 2MS and 3MS, 3MS is an expanded version, which is better in predicting functional outcomes, according to a study done on stroke patients.[15] The presence of comorbid depression may also affect the cognition assessment in these patients.[16,17]

We did a Google and Pub med search with the terms "Modified Mini-Mental Score and HIV", "Modified Mini-Mental Score and AIDS" and "Modified Mini-Mental Score and PLHIV" but could not find any studies. We also did not find any study checking both IHDS and 3MS together in the same group of patients to evaluate cognitive disorders. Therefore, we compared 3MS and IHDS in screening for HAND in patients suffering from HIV disease.

Material and Methods

We studied HIV-positive patients coming to the OPD in the Department of Medicine, King George's Medical University, Lucknow, India, from September 2015 to September 2019.

Case selection
Inclusion criteria
We included patients with HIV disease aged more than 18 years and up to 60 years of age in full Glasgow Coma Scale (GCS) (fully oriented to time, place, and person) without any signs of meningeal irritation and raised intracranial tension in the study. This study included all the patients giving consent for the study. Also, we studied a similar number of age-, sex-, and education- matched healthy controls, who gave consent for the study.

Exclusion criteria
We excluded patients having any history of head injury, history of known psychiatric illness, history of any substance abuse in the past 1 year, or those with education below the 8th standard of schooling from the study.

Sample size
According to the Uttar Pradesh State AIDS Control Society, the adult prevalence of PLHIV in the state of Uttar Pradesh is 0.12%.[16]

The population of Lucknow in 2015 was around 32 lacs. PLHIV visiting ART center in the institute in 1 year is around 5000. Most of these are adults. Most of these present due to complications associated with HIV infection. Hence, we estimated that there would be around 1000 people who would be otherwise free of other complications of HIV disease, which would thus fit into the inclusion criteria of this study. Hence, we did a sample size calculation based on a confidence interval of 95%, a confidence level of 5, a population size of 1000, and got a sample size of 278.

Methods
The authors used 3MS and IHDS tests to assess the cognitive functions of 200 patients suffering from HIV disease according to the National AIDS Control Organization (NACO) testing guidelines and that of 200 age-, education-, and sex-matched healthy controls.[18-20]

Once enrolled, investigators noted their medical history and examination after taking their informed written consent. Also, we took the history of the patients, in particular regard to any opportunistic infections and the subsequent treatment taken in the past, and excluded such patients from the study. Investigators included only those patients, who were fluent in the English language. We carried out laboratory investigations at the ART center as per the NACO program, which includes hemoglobin, complete blood counts, serum electrolytes, renal and hepatic function tests, and some additional tests like serum vitamin B12 levels and thyroid function tests. The authors excluded all patients, with abnormal thyroid function tests or vitamin B12 levels and did a CT scan of the head and excluded from the study, all those with an abnormal CT head. We also administered Patient's Health Questionnaire-9 (PHQ-9) to these patients for the assessment of depression as it could be a confounding factor.[21] Our study included informed consent for all the study participants. SK administered the tests, and RT and DH confirmed them, one of whom is a trained neurologist, and the other is a well-experienced infectious disease specialist. The institutional ethical committee has approved this study (Approval number: 77th ECM II B- Thesis/P6).

Data analysis
Microsoft IBM SPSS version 20 (Statistical Product and Service Solutions) analyzed the data. We calculated the mean and standard deviation for IHDS and 3MS and also for the individual parameters of these tests. We used the Chi-square test for comparing between categorical data and calculated frequency, and percentage for different clinical and demographic variables.

Results

Out of 270 patients contacted, only 240 consented to the study. Out of these, we excluded 40 patients based on CT head findings or abnormalities on other parameters of exclusion criteria. Out of 200 patients, 65% were male, and the remaining were female. The education level of most of them (89.5%)

was between 8th and 12th classes, and ages were between 25 and 50 years (81.5%) [Table 1].

As per 3MS, cognitive impairment occurred in 42 (21%) HIV patients (3MS Score <79; mean 3MS score of 76.24 ± 1.51), and 158 (79%) HIV patients were not impaired (3MS score ≥79) having a mean 3MS score of 87.02 ± 4.16. According to IHDS, however, neurocognitive impairment occurred in 185 (92.5%) HIV patients (Dementia score ≤10, mean score of 8.45 ± 0.88). The remaining 15 (7.5%) patients were not cognitively impaired (Dementia score >10) and had a mean score of 11.13 ± 0.35.

The mean 3MS score of controls was 87.31 ± 4.18, and the average IHDS score was 9.7 ± 0.99.

Figure 1 depicts the mean of individual parameters of IHDS, and Figure 2 shows the mean of individual parameters of 3MS.

Eighty-eight (44%) patients were minimally depressed, 105 (52.5%) were mildly depressed, and the remaining 7 (3.5%) patients were moderately depressed according to PHQ-9.

Discussion

The investigators planned this study to find out the variation in cognitive impairment by two different assessment methods. As in the previous studies, in our study, also, the males outnumbered the females. We may explain this by the fact that the disease is more prevalent in the male population or because the males might be utilizing the health care resources to a greater extent in comparison to the females.[7,22] In our study, maximum people had an education between 8th and 12th standard, and the graduates and postgraduates were very less and these may be due to the fact that lesser education might be a risk factor for HIV disease and as such the disease prevalence is higher in the underprivileged community. This fact is also in accordance with the previous studies.[7,23,24] We did not enroll patients with less than the 8th standard of education because they might not have been able to follow the instructions of the 3MS and IHDS examination properly.

An important confounding factor could have been the prevalence of depression among the study population. Only 7% of our patients had moderate depression, and none of them had severe depression. As HIV is a multisystem disease causing multiple constitutional symptoms like poor appetite, tiredness, and difficulty in concentration, a substantial proportion of patients seen were having minimal depression in PHQ-9. Hence, it may be possible that investigators may misinterpret these constitutional symptoms as depression, and as such, none of the patients had major depression, which could have been a confounding factor in the assessment of dementia. Previous studies have reported the presence of depression in a higher percentage of patients, and the presence of constitutional symptoms in these patients may be one of the reasons for over-reporting of depression in these patients.[11,16,17,25,26]

The prevalence of HAND in PLHIV in different studies worldwide varies between 5% and 85%.[7-10,27,28] Different studies published from India, report a very low prevalence of HAND (<10%). However, a study conducted in Chennai and Bangalore and another in Ghaziabad in India showed the prevalence to be between 50% and 60%.[10,29] India has a greater prevalence of the clade C virus, a natural variant of the Tat protein, which promotes viral replication directly, and this fact may be the reason for the low prevalence of HAND in India.[10] However, the mode of assessment method varies among different studies. Most of the studies employ IHDS as the assessment method. In our study, when assessed using 3MS, we found that neurocognitive impairment occurs in around one-fourth of all HIV patients. However, on applying IHDS to the same cohort, we found that neurocognitive impairment exists in a very high percentage (>90%) of patients. On analyzing the individual parameters of IHDS in HIV patients [Figure 1], we found the psychomotor speed to be the most affected parameter in the patients examined. Before giving marks during testing of this modality, investigators had fully explained the way of performing this maneuver to the participants, in participants' language and followed the proper protocol, but still, this maneuver was difficult to perform and understand. Therefore, this might be a reason for getting poor results of this modality and over-catching of psychomotor dysfunction and in turn, causing overdiagnosis of cognitive impairment by IHDS. The actual prevalence of HAND might be less in India in comparison to the worldwide prevalence,
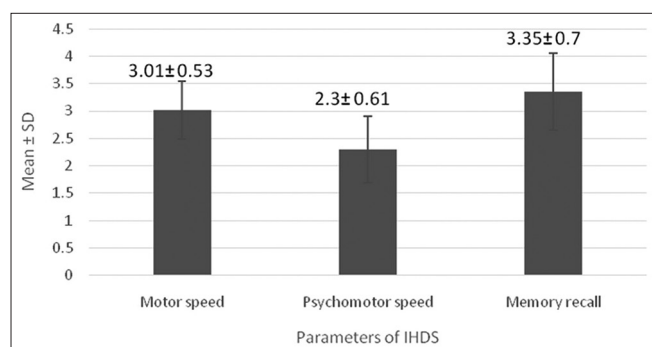

Figure 1: Mean of individual parameters of IHDS in HIV patients
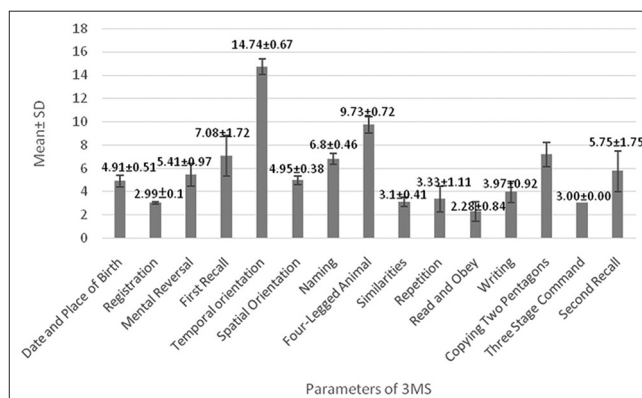

Figure 2: Mean of individual parameters of 3MS in HIV patients

Table 1: Demographic and clinical profile of patients of HIV disease and healthy controls							
Characteristic	Male (*n*=130 cases, *n*=154 controls)		Female (*n*=70 cases, *n*=46 controls)		Total (*n*=200 cases, *n*=200 controls)		Statistical significance	
	No.	%	No.	%	No	%	P	P of cases versus controls of males and females
Age (Cases)								
<25 Yrs	7	5.4	9	12.9	16	8.0	0.177	0.061, 0.277
25-50 Yrs	109	83.8	54	77.1	163	81.5		
>50 Yrs	14	10.8	7	10.0	21	10.5		
Age (Controls)								
<25 Yrs	19	12.3	3	6.5	22	11	0.039	
25-50 Yrs	125	81.2	35	76.1	160	80		
>50 Yrs	10	6.5	8	17.4	18	9		
Education (Cases)								
8th-12th	121	93.1	58	82.9	179	89.5	0.204	0.178, 0.364
Graduate	8	6.2	9	12.9	17	8.5		
Postgraduate	1	0.8	3	4.3	4	2.0		
Education (Controls)								
8th-12th	135	87.7	43	93.5	178	89	0.387	
Graduate	14	9.1	3	6.5	17	8.5		
Postgraduate	5	3.2	0	0	5	2.5		
CD4 Count (Cases)								
≤500	90	69.2	35	50.0	125	62.5	0.202	-
>500	40	30.8	35	50.0	75	37.5		

due to the presence of the clade C virus in India. However, we did not carry out the clade typing of the cases; hence, this is an assumption only. Another fact validating this assumption might be the average IHDS score, in healthy controls of similar educational status, gender, and age, of 9.73 ± 1.00, which is again lower than the normal IHDS score. The mean 3MS score of controls, on the other hand, was 87.56 ± 4.26, which was well within the normal 3MS range. We even scored the IHDS omitting the psychomotor speed examination, using a scaled cut-off score of <=6 for cognitive impairment and detected cognitive impairment in only around half of the patients, according to this criteria. Hence, the IHDS score, *per se*, might be giving inflated results for cognitive impairment.

There are certain domains of cognitive functioning like motor functioning, attention, processing speed, executive functioning, learning, verbal memory, reasoning, verbal fluency which may be more often affect patients suffering from HIV disease.[30] Hence, testing for these particular domains of cognitive function using advanced neurocognitive tests would be a better choice for detecting HAND.

Therefore, we may conclude that 3MS may be more accurate for catching the impairment in different modalities of cognition in patients suffering from HIV disease. Though IHDS may take a slightly lesser time in diagnosing cognitive impairment in HIV patients, however, due to the possibility of overdiagnosis of cognitive impairment when tested using IHDS, we propose that one may use 3MS for screening for HAND and later on employ advanced neurocognitive tests, when time permits. Knowing and administering 3MS, which is freely available and accessible may

be a better choice for screening for cognitive impairment in HIV patients, in outdoor settings by neurologists as well as by primary care physicians, who might encounter such patients more often in their practice. Preferring 3MS over IHDS for the assessment of neurocognitive impairment in HIV patients is a new concept, which may give a better estimate of neurocognitive impairment.

Also, the authors conclude that if researchers develop a new scale containing IHDS parameters and parameters of 3MS, the scale would be more equipped to catch early cognitive impairments.

Limitations

We did not employ advanced neurocognitive tests and also did not perform the clade typing of the cases.

Key points

IHDS may over diagnose neurocognitive impairment in HIV patients.

3MS may be more accurate for detecting neurocognitive impairment in HIV patients.

Scale combining 3MS and IHDS may be better for screening for cognitive impairment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials

will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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