Prevalence of HIV Associated Neurocognitive Disorder using Modified Mini Mental State Examination and its Correlation with CD4 Counts and Anti-retroviral Therapy

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Abstract

Introduction: HIV Associated Neurocognitive Disorder (HAND) is still prevalent even in the ART (Anti-Retroviral Therapy) era. It may have some association with CD4 counts and Anti-Retroviral Therapy. The prevalence of HAND in HIV-patients, was, therefore studied in the context of ART and CD4 counts.

Methods: Modified Mini Mental State Examination scores of 200 (65% males) HIV-positive patients and 200 controls were analyzed in the context of ART and CD4 counts.

Results: Maximum number of participants were educated between 8th-12th class (89.5%), aged between 25-50 years (81.5%) and a higher proportion of males had a CD4 count ≤500 (69.2%) (p=0.007). Using 3MS, 21% patients (mean 76.24±1.51) and none of the controls were found to be neurocognitively impaired. Mean scores of patients with CD4 counts≤500(82.54±5.58) were lesser in comparison to those of patients with CD4 counts>500 (p<0.001). Those with an ART duration of <48 months had a lower score in comparison to those with an ART duration of >72 months (p=0.005).Most decrease from maximum value was seen in similarities (48.3 %), second recall (36.1 %), repetition (33.4 %), copying two pentagons (28.3 %), read and obey (24.0 %), mental reversal (22.7 %) and first recall (21.3%) parameters of Modified Mini Mental State Examination.

Conclusions: HAND was less prevalent in the present study in comparison to past literature. CD4 counts and ART duration had an inverse association with the degree of cognitive impairment. The parameters of Modified Mini Mental State Examination showing maximum impairment may be compiled to form a short screening questionnaire.

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Introduction

HIV (Human Immunodeficiency virus) disease is a major problem and much prevalent disease worldwide, more so in the low and middle income countries. According to the United Nations Programme on HIV and AIDS (UNAIDS) estimate, there were approximately 36.9 million people living with HIV/AIDS (Acquired Immunodeficiency Virus) in 2015.[1] India has the third highest number of people living with HIV disease in the world.[2] There has been a steady decline in number since 2007 with numbers coming down from 2.23 million to 2.12 million in 2015.[3]

HIV enters the central nervous system (CNS) after initial infection and is responsible for a range of neuropsychiatric complications directly or through associated immune activation.[4] Brain-related problems in HIV patients include HIV associated neurocognitive impairment (HAND) and opportunistic infections.

Cognition is a mental process involved in judging, knowing, learning, perceiving, recognizing, remembering, thinking, and understanding that leads to the awareness of the world around us. It is involved in acquisition and understanding of knowledge, formation of beliefs and attitudes and in the decision making and problem solving.[5] Among these cognitive domains, the HIV infection most prominently affects motor functioning, attention, processing speed, executive functioning, and memory and this HIV related neurocognitive impairment can be classified into asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD), depending on the disease severity.[6] HAND is an important cause of morbidity.[7] Hence, it is necessary to study the prevalence of HAND in people living with HIV disease (PLHIV), to employ some interventions to manage this complication. HIV-associated neurocognitive impairment may be more severe in people at their

Table 1: Modified mini mental state examination scores of patients with HIV disease in relation to the CD4 counts and duration of ART

SN	Predictor	3 MS score	
		Mean	SD
1.	CD4 count		
	≤500 (n=125)	82.54	5.58
	>500 (n=75)	88.44	3.99
	t=8.003; p<0.001 using t-test		
2.	Duration of ART (n=182)		
	Less than 48 months (n=82)	83.10	5.76
	48-72 months (n=39)	85.15	6.40
	More than 72 months (n=61)	86.11	5.00
	F=4.415; p=0.005 using ANOVA		

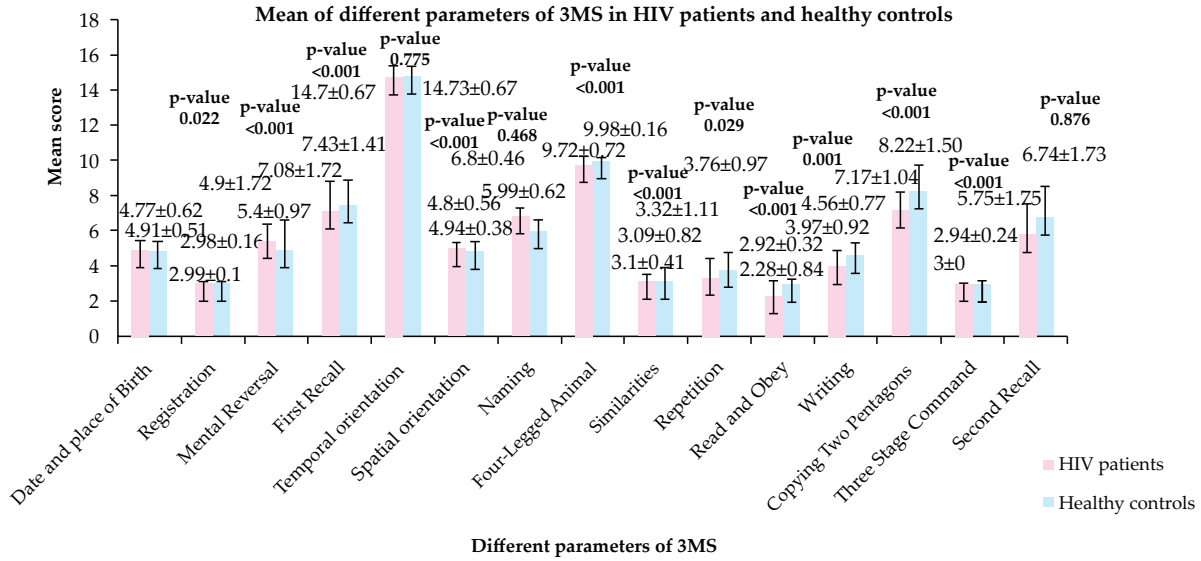

Fig. 1: Means of different parameters of Modified Mini Mental State Examination in HIV patients and in healthy controls

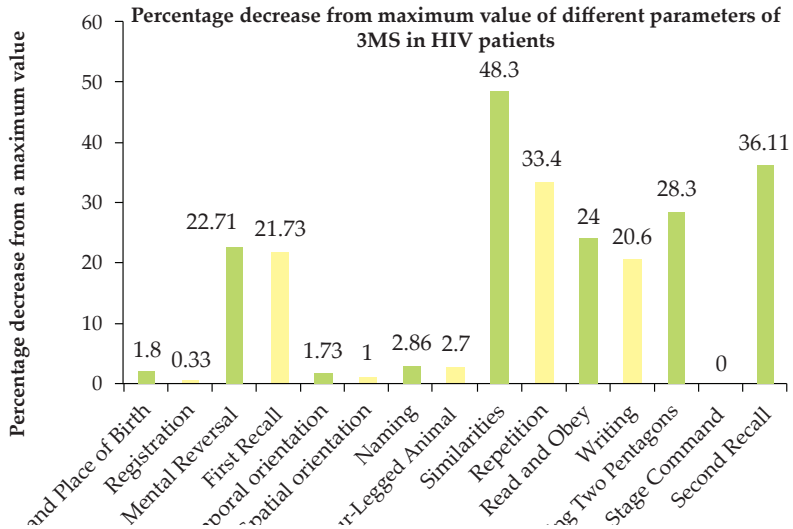

Fig. 2: Percentage decrease from maximum value of different parameters of Modified Mini Mental State Examination in HIV patients

extremes of age and in those with more severe disease, measured through lesser CD4 counts and the more time since the onset of HIV disease.[8-10]

Neurocognition can be tested by various methods and Mini Mental State Examination (2S) and Modified Mini Mental State Examination (3MS) are two such methods.[11,12] Among Mini Mental State Examination and Modified Mini Mental State Examination, Modified Mini Mental State Examination is an expanded version, which has been found to be better in predicting functional outcome in a previous study.[12]

King George's Medical University (KGMU), Lucknow, India, is a tertiary care center in North India, which serves as a referral center to patients suffering from HIV disease from North India and also some patients from other parts of the country as well.

Hence, we assessed the prevalence of HIV Associated Neurocognitive Disorder (HAND) in HIV patients presenting to the outdoors of King George's Medical University, Lucknow, India and the factors affecting HAND in the PLHIV. The presence of co-morbid depression may also affect the cognition assessment in these patients and this was also studied.[13,14]

Materials and Methods

The study was conducted in the Department of Medicine, KGMU, Lucknow, India on HIV positive patients visiting the outdoors of KGMU, Lucknow, India, from September 2015 to September 2016.

Participants

Patients with HIV disease aged more than 18 years and in full GCS (fully oriented to time, place and person) without any signs of meningeal irritation, raised intracranial tension or a history of head injury, were included in the study. All the patients giving consent for the study were included. Those people, who were educated below 8th standard, were excluded from the study. Age, sex and educational status matched healthy control participants, who gave consent for the study, were also included. The controls were taken from among hospital staff members, whose HIV status was shown to be negative.

Procedure

The Modified Mini Mental State Examination test was used to assess the cognitive functions of 200 patients suffering from HIV disease according to the NACO testing guidelines.[15,16] Since, previous researchers have shown that at a cut off of 79, the sensitivity and specificity of detecting cognitive impairment is between 98-100 and 70-81 respectively, hence, we chose a cut off of 79 for defining cognitive impairment. The patients were defined as cognitively impaired, if they had a total 3MS score of <79.[17,18] The test was administered to the patients by means of personal interview by the investigator, who is a resident doctor and were confirmed by another

Table 2: Relationship of different parameters of 3 MS score with CD4 counts and the duration of ART

Parameter of 3MS score	3MS parameter in CD4 ≤500 (n=125)	3MS parameter in CD4 >500 (n=75)	t value and p*	3MS parameter in ART <48 months (n=82)	3MS parameter in ART 48-72 months (n=39)	3MS parameter in ART >72 months (n=61)	F value and p#
Date and place of birth	4.90 ± 0.53	4.92 ± 0.49	-0.213, 0.832	4.89 ± 0.57	5.00 ± 0.00	4.95 ± 0.38	1.946, 0.123
Registration	2.99 ± 0.09	2.99 ± 0.12	0.365, 0.715	2.99 ± 0.11	3.00 ± 0.00	2.98 ± 0.13	0.285, 0.836
Mental reversal	5.23 ± 0.90	5.69 ± 1.03	-3.329, 0.001	5.24 ± 0.95	5.54 ± 1.02	5.46 ± 0.96	1.593, 0.215
First recall	6.60 ± 1.70	7.87 ± 1.46	-5.379, <0.001	6.78 ± 1.71	6.82 ± 1.92	7.38 ± 1.52	3.355, 0.020
Temporal orientation	14.58 ± 0.81	14.99± 0.12	-4.301, <0.001	14.63± 0.78	14.77± 0.63	14.77± 0.62	0.858, 0.426
Spatial orientation	4.97 ± 0.28	4.91 ± 0.50	1.112, 0.267	5.00 ± 0.00	4.90 ± 0.50	4.89 ± 0.55	1.431, 0.235
Naming	6.73 ± 0.51	6.91 ± 0.34	-2.685, 0.008	6.73 ± 0.50	6.79 ± 0.47	6.82 ± 0.47	1.768, 0.155
Four-legged animal	9.70 ± 0.74	9.77 ± 0.69	-0.732, 0.465	9.74 ± 0.70	9.64 ± 0.87	9.75 ± 0.67	0.225, 0.155
Similarities	3.07 ± 0.38	3.15 ± 0.46	-1.238, 0.217	3.06 ± 0.43	3.13 ± 0.52	3.11 ± 0.32	0.482, 0.695
Repetition	3.18 ± 1.00	3.56 ± 1.24	-2.352, 0.020	3.68 ± 0.90	4.13 ± 0.86	3.38 ± 1.16	1.446, 0.231
Read and obey	2.11 ± 0.87	2.55 ± 0.70	-3.658, <0.001	2.11 ± 0.92	2.23 ± 0.84	2.41 ± 0.74	3.023, 0.031
Writing	3.61 ± 0.88	4.57 ± 0.62	-8.347, <0.001	3.68 ± 0.90	4.13 ± 0.86	4.18 ± 0.92	4.841, 0.003
Copying two pentagons	6.99 ± 1.14	7.47 ± 0.76	-3.204, 0.002	7.21 ± 1.06	7.10 ± 1.12	7.15 ± 1.01	0.142, 0.868
Three stage command	3.00 ± 0.00	3.00 ± 0.00	-, -	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	-, -
Second recall	5.27 ± 1.73	6.55 ± 1.47	5.327, <0.001	5.38 ± 1.63	5.69 ± 1.88	6.16 ± 1.75	2.810, 0.041

All values: Mean ± SD; *t test; #ANOVA

investigator who is a neurologist. Once enrolled, the history and examination of the patients was noted. History of the patients was also taken, in particular regard to any opportunistic infections and subsequent treatment taken in the past. Laboratory investigations were done at ART center as per the NACO programme, which included hemoglobin, complete blood counts, serum electrolytes, renal and hepatic function tests and some additional tests like serum vitamin B12 levels and thyroid function tests. Those participants, who had vitamin B12 levels of less than 200 or deranged thyroid function tests, were excluded from the study. A CT scan of the head was also done and those with an abnormal CT head were excluded from the study. Patient's health questionnaire-9 (PHQ-9) was also administered to these patients for the assessment of depression as it could be a confounding factor.[19] All the patients who were found to be moderately severe or severely depressed were excluded from the study. Two hundred age, sex and education matched healthy controls were also included in the study. A written informed consent was taken from all the study participants. The study was approved by the institutional ethical committee of King George's Medical University, Lucknow, India (Approval number: 77th ECM II B-Thesis/P6).

Data analysis

The data was analyzed using Microsoft IBM SPSS version 20 (Statistical Package for the Social Sciences). The means, medians and standard deviations were calculated for different demographic variables. The means and standard deviations were calculated for Modified Mini Mental State Examination total score and different individual parameters of Modified Mini Mental State Examination. Frequency and percentage was calculated for different demographic and clinical parameters and significance was tested between frequencies of different variables using Chi square tests. For comparison among different means, T-test and ANOVA were used.

Results

Out of 200 patients, 65% were males and the remaining were females. Sixteen (8%) patients [7 (5.4%) males and 9 (12.6%) females] were of <25 years of age, 21 (10.5%) patients [14 (10.8%) males and 7 (10%) females] were of >50 years of age, but maximum patients [163 (81.5%) with 109 (83.8%) males and 54 (77.1%) females], belonged to an age group between 25-50 years (p=0.056). Most of the patients [179 (89.5%), 121 (93.1%) males and 58 (82.9%) females] had an education between 8th-12th standard and only 17 (8.5%) [8 (6.2%) males, 9 (12.9%) females], were graduates and 4 (2%) [1 (0.8%) male, 3 (4.3%) females], were postgraduates (p=0.056). CD4 counts of ≤500 were observed in 90 (69.2%) males and 35 (50%) females [125 (62.5%) total cases] and the remaining people had CD4 counts of >500 (p=0.007) (using Chi-square tests).

The median CD4 count of the cases was 429. Using Modified Mini Mental State Examination, neurocognitive impairment was seen in 42 (21%) of the HIV patients (mean score 76.24±1.51) and 158 (79%) HIV patients were not found to have a neurocognitive impairment (mean score 87.02±4.15).

There were 200 controls. Mean Modified Mini Mental State Examination score of controls was 87.62±4.23 (p-value for difference from cases was <0.001).

The 3 MS score of patients with HIV disease in relation to CD4 counts and the duration of antiretroviral therapy is mentioned in Table 1.

There were 18 patients, who were not on ART, as they were new patients with a high CD4 count, in whom ART had not yet been started, in accordance with the National guidelines of India, who had a mean Modified Mini Mental State Examination score of 86.13±5.43. The median CD4 count of these patients was 579.

The mean of different parameters of Modified Mini Mental State Examination in HIV patients and healthy controls is mentioned in Figure 1. The differences in between means were also calculated using independent samples T-test and the p-values are depicted in Figure 1.

Of the 15 parameters of Modified Mini Mental State Examination, for all

except one item (three stage command) the mean scores were lower than normal value. The mean scores ranged between 2.99±0.10 (Registration) and 14.74±0.67 (Temporal orientation) (Figure 1).

The percentage decrease from maximum value of different parameters of Modified Mini Mental State Examination is mentioned in Figure 2.

The maximum decrease from the highest achievable value was seen in similarities (48.3 %), second recall (36.1 %), repetition (33.4 %), copying two pentagons (28.3 %), read and obey (24.0 %), mental reversal (22.7 %) and first recall (21.3%) parameters of Modified Mini Mental State Examination (Figure 2).

The relationship of different parameters of 3 MS score with CD4 counts and the duration of ART is depicted in Table 2.

Discussion

Around two-thirds of all patients were male and the remaining were females. This is consistent with the previous studies and may be either because the disease is more prevalent in the male population or because males may be utilizing the health resources to a greater extent in comparison to the females.[20,21] In our study, maximum people had an education between 8th and 12th standard and the graduates and post graduates were very less and this 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 underprivileged community. This fact is also in accordance with the previous studies.[22] However, significantly higher proportion of males had a CD4 count ≤500, which may be because, the disease may be more advanced in males as compared to the females due to increased chances of acquiring disease due to high risk behaviour.

HAND in different studies worldwide has been shown to be seen in approximately 50% of all HIV infected individuals, with some studies showing a prevalence of as high as 85%.[23,24] In different studies published mainly from Southern and Western parts of India, a very low prevalence of HAND (<10%) is reported. But a study conducted in Chennai and Bangalore in India, showed the prevalence to be between 50 to 60%. Clade C virus, a natural variant of the Tat protein, which promotes viral replication directly, has been shown to be greater in India, which could explain the low prevalence of HAD in India.[25] In our study, around one-fourth of all patients with HIV disease were found to be neurocognitively impaired when tested using Modified Mini Mental State Examination, which could be explained by the presence of Clade C virus in India.

In the present study, those patients who had higher CD4 counts and a greater duration of ART, were found to have a lesser neurocognitive impairment, which shows that lesser burden of disease and early initiation of ART prevents neurocognitive decline in these patients. It was also observed that HIV-infected individuals who never experienced low CD4 cell counts were relatively protected from neurocognitive impairment in comparison to those with a history of severe immune-suppression. A possible pathogenic mechanism suggested could be that a lower level of CD4 T-cells may allow a greater entrance of viruses inside the Central Nervous System. Similar observations have been there in some previous studies, though there are a few studies, which are not in accordance with this finding.[26-31] Those who were not on ART had a very high Modified Mini Mental State Examination score, probably because most of these patients were having a higher CD4 count and were new patients and had probably not experienced a nadir of CD4 counts. According to the national guidelines of India till September 2016, ART was started only if CD4 count was below 350 cells/cc or if the patient was in clinical stage 3 or 4 of WHO staging. So, better immune competence might be the reason for these patients having a higher Modified Mini Mental State Examination score.

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 affected in patients suffering from HIV disease and certain domains like naming and visuospatial functions may be relatively preserved in these patients depending on the severity of cognitive deficit.[6,32] However, some studies have detected impairment of visuospatial functions in HAND.[33] Hence, testing for these particular domains of cognitive function using advanced neurocognitive tests would be a better choice for detecting HAND. It took around ten to twelve minutes to administer Modified Mini Mental State Examination to these patients. However, for screening purposes, we may need a smaller test, which takes lesser time to screen for cognitive dysfunction.

Since, certain parameters of Modified Mini Mental State Examination like similarities, second recall, repetition, copying two pentagons, read and obey, mental reversal and first recall were found to be most affected in patients suffering from HIV disease in our study, so, it is proposed that a shorter version comprising these parameters may be a useful tool for screening people living with HIV disease.

Conclusions

The prevalence of HAND in this study was lesser in comparison to the previous studies. CD4 counts and duration of ART were inversely associated with cognitive impairment in PLHIV. Since, certain parameters of Modified Mini Mental State Examination like similarities, second recall, repetition, copying two pentagons, read and obey, mental reversal and first recall were found to be most affected in patients suffering from HIV disease in our study, so, it is proposed that a shorter version comprising these parameters may be a useful tool for screening patients for HAND.

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