Cognitive Assessment of Young Adults Before and After Initiation of Combination Antiretroviral Therapy

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Research Article

Keywords: Antiretroviral treatment, Cognitive functions, HIV, MoCA test, Neurocognitive disorders

Posted Date: April 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-467874/v1>

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Abstract

Background: This study aimed to evaluate cognitive functions and the factors affecting them in naive HIV-positive patients by Montreal Cognitive Assessment (MoCA) test before and after the initiation of combination antiretroviral therapy.

Method: HIV-positive, treatment-naive patients monitored between January-June 2017 were included in the study. MoCA test was performed at the beginning and the 6th month of the treatment.

Findings: Forty male patients were included in the study. The mean age was calculated as 29.1 ± 4.0 . When the factors affecting the MoCA score were examined, there was a significant relationship between the education level and the MoCA score. Smoking, alcohol and substance did not have a meaningful impact on baseline MoCA values. A significant correlation was found between CD4 count and HIV RNA level and attention function. There was a significant increase in the total MoCA score and the MoCA subgroup scores at the end of the 6th month of the treatment.

Conclusion: MoCA test is one of the practical tests that can be applied in a short time period and it was found useful in evaluating the changes in the cognitive functions of HIV positive patients during antiretroviral treatment.

Background

The presence of cognitive disorders in the human immunodeficiency virus (HIV) infected individuals has been known for a long time. A complete neuropsychological evaluation is the gold standard method for the diagnosis of HIV-related cognitive impairment (HAND). However, such tests require specially trained personnel, specialized centers and testing takes a long time¹. Montreal Cognitive Assessment (MoCA) is a test originally developed to screen cognitive impairment in geriatric population at risk of early dementia. MoCA tests a wide range of cognitive domains, including memory, attention and frontal executive functions, which are often affected in HIV-infected patients. Accordingly, it is sensitive in detecting mild cognitive impairments. Also, it can be applied both for baseline and follow-up assessments^{2,3}.

The use of antiretroviral therapy (ART) has resulted a significant decrease in HAND incidences^{4,5}. Combination of antiretrovirals, which have better penetration through the blood-brain barrier, might be more effective in the treatment of HAND⁶.

Our study aimed to evaluate the cognitive functions of HIV-infected patients in our clinic through MoCA test, determine the factors affecting cognitive functions, and compare the cognitive functions before and after the treatment.

Materials And Methods

The study was conducted prospectively between 1 January and 1 June 2017 in Şişli Hamidiye Etfal Training and Research Hospital. Fifty-two HIV-positive patient were included in the study. Inclusion criteria were; being between the ages of 20-35, being diagnosed HIV recently and planning starting treatment. Exclusion criteria were; having neurological or psychiatric comorbid disease, systemic infection, metabolic disorder, anemia, hypo-hyperthyroidism, positive syphilis serology, history of substance or alcohol abuse, head trauma or central nervous system infection. Beck depression scale was used to exclude patients with depression. Patients with more than nine points were excluded due to possible depressive states. The study was reviewed and approved by the Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital in Istanbul, Turkey.

The patients with eligible criteria were evaluated just before the initiation of the treatment. Montreal Cognitive Assessment Scale (MoCA) was used to evaluate cognitive functions. It was performed by the same physician and cognitive impairment was evaluated by using the suggested cut-off score of ≤ 21 for our country⁷. The patients' age, gender, education level, smoking habit, alcohol and substance use, CD4 + T lymphocyte count, HIV RNA level, toxoplasma serology were recorded and the patients were classified into groups according to these parameters. To determine the effects of education on MoCA test, the patients were divided into two groups, such as university graduates and lower education. The patients were divided into groups by levels of CD4 + T lymphocyte (over 500 cell/uL or below) and HIV RNA (over 10^4 copies / ml and below) to show their effects on MoCA scores. MoCA scores of Toxoplasma IgG (+) and IgG (-) groups were compared to assess the effects of previous toxoplasma infection on cognitive functions.

The patients whose treatment was started and who had treatment compliance were re-evaluated at the 6th month of the treatment. Depressive symptoms were evaluated again with the Beck Depression Scale, and MoCA test was performed. Follow-up CD4 + T lymphocyte and HIV RNA levels were recorded. MoCA test results of the patients were compared with their pre-treatment values. MoCA scores of viral suppressed and non-suppressed groups were compared, and the changes in MoCA scores in these two groups were examined.

MoCA Test

MoCA test evaluates attention, concentration, executive functions, memory, language, visual structuring skills, abstract thinking, calculation, and orientation. The application duration of the test is approximately 10 minutes. The highest score that can be obtained from the test is 30.

Statistical analysis

Average, standard deviation, median, lowest, highest, frequency and ratio values were used in the data's descriptive statistics. The distribution of variables was measured by Kolmogorov Smirnov Test. Mann-Whitney U test was used in the analysis of independent quantitative data. Wilcoxon test was used to analyze dependent quantitative data. Spearman Correlation Analysis was used in the correlation analysis. P-values were corrected for multiplicity. SPSS 22.0 program was used in the analysis.

Results

A total of 52 patients were included in the study. Two female patients were excluded from the study because of the possibility of affecting the sample distribution. Patients with elevated Beck Depression Scale, positivity in syphilis serology and diagnosed with bipolar disorder were also excluded. The study continued with a total of 40 patients.

All of the patients were male, and the mean age was 29.1 ± 4.0 (age range: 25-35). The patients' baseline median CD4 + T lymphocyte count was determined as: 515.0, [Interquartile range (IQR) : 374], baseline median HIV RNA level determined as 75,100 copies/ml [Interquartile range (IQR) :207.850].

Baseline Assessment

The mean baseline MoCA score of the patients was 22.6 ± 3.9 . In 11 patients (27.5%) it was below the normal value, and the most affected cognitive function was delayed recall and attention functions, respectively.

The baseline MoCA score was significantly higher in university graduated and higher education groups than in lower graduated education groups ($p \leq 0.05$) (Figure 1). MoCA Visual-Spatial / Executive Functions Score, MoCA Attention Score, MoCA Abstract Thinking Score; the subgroups of MoCA, were significantly higher in university graduated and higher education groups. No relationship was found between smoking, substance or alcohol use, and the MoCA score.

There was no significant difference between the total MoCA score of the high (%42.5) or low HIV RNA level group (%57.5). However, the low HIV RNA level group's attention score was significantly higher than the higher HIV RNA level group ($p < 0.05$). The relationship between the baseline HIV RNA and total MoCA scores and MoCA subgroup scores is presented in Table 1.

When the groups were compared according to the CD4 + T lymphocyte levels, no significant difference was found in the total MoCA score. However, the attention score was significantly higher in the group with a high CD4 + T lymphocyte (%52.5) level than the group with low CD4 + T lymphocyte (%47.5) level (Table 2).

Ten patients included in the study had a toxoplasma infection history. When the groups with negative and positive toxoplasma serology were compared, no significant difference was found in terms of cognitive functions.

Follow-up Assessment

Follow-up MoCA score increased significantly compared to the baseline MoCA score ($p < 0.05$). MoCA score was found below the normal value in 3 patients (7.5%) at the 6th month of the treatment. When the changes in MoCA subgroups were examined, it was observed that there was an improvement in all cognitive functions except the orientation function (Table 3, Figure 1)

There was no significant difference between the MoCA scores of the patients whose HIV RNA fell below 50 copies/ml and those whom HIV RNA did not fall below the threshold. Patients were also examined in terms of changes in MoCA scores. The change in the total MoCA score and delayed recall subgroup score of the group whose HIV RNA level was below 50 copies/ml was significantly higher than the group whose HIV RNA level did not fall below 50 copies/ml ($p < 0.05$).

When the two groups that CD4 + T lymphocyte counts below and above 500 cells / μ L were compared, no significant difference was found between the follow-up MoCA scores.

Discussion

HIV, which is known to have effects on many systems of the body, especially the immune system, also affects the central nervous system from the early stages of the disease. Cognitive impairment caused by the virus may vary clinically from asymptomatic to severe cases such as dementia. The positive effect of ART on cognitive functions has been supported by many studies. It has been reported that ART usage is particularly effective on improvement of attention functions, verbal rationality and visual and executive functions⁸⁻¹². In our study, we used the MoCA test to assess neurocognitive impairment. The most impacted cognitive functions were delayed recall and attention functions. The numbers of patients with cognitive disorders before and after the treatment were 11 (27.5%) and 3 (7.5%), respectively. After the treatment, improvements were observed in the patients' cognitive functions including visual/spatial executive functions, naming, language, abstract thinking, delayed recall, and attention functions. Significant improvement at MoCA scores after ART indicates that ART had positive effects on the cognitive functions, as shown in the literature.

Differences in educational experiences may result in lower performance on neuropsychological tests. In a study, cognitive impairment was found at a rate of 17% in HIV-positive patients with a high school and higher education degree, and 38% in others receiving education below high school¹³. Education level also affects MoCA scores¹⁴. In our study, MoCA scores were assessed according to the education level, and the scores were significantly higher in the university and higher educated groups.

Studies show that smoking affects cognitive functions, especially learning and memory^{15,16}. Alcohol use in HIV-infected patients causes rapid progression of HIV infection and increases the HIV virus' negative effects on cognitive functions; especially executive functions and reaction time^{15,17}. In our study, no relation was found between smoking, alcohol use, and cognitive functions.

Regarding the relationship between the HIV-related conditions and cognitive functions, studies show that low CD4 count is one of the most important factors^{18,19}. In our study, there was no significant difference between the lower and higher CD4 count level groups in terms of total MoCA scores, but the attention scores were significantly higher in higher CD4 count level group.

Different results were found in studies examining the relationship between plasma HIV RNA level and cognitive functions. In a study involving 140 patients in United States of America, patients were divided into three classes according to their viral loads, and their cognitive functions were compared by neuropsychological tests. There was no significant difference between these three groups in terms of cognitive functions²⁰. In a study from Australia, neuropsychological tests were applied to groups with and without viral suppression, and no significant difference was found between the two groups in terms of cognitive functions²¹. In another study, HIV RNA values above 4.5 log 10 copies were found to be associated with increased risk of cognitive disfunction²². In our study, there was no significant difference in MoCA tests of the groups separated according to HIV RNA level, but MoCA subgroup scores measuring attention were found to be significantly higher in the low viral load group. At the sixth month of treatment, it was seen that viral suppression did not make a significant difference in terms of cognitive functions. However, the change in the total MoCA score (difference in the follow-up baseline MoCA score) and the delayed recall subgroup score in the group with viral suppression were found to be significantly higher than the group without viral suppression (figure 2).

Although virological suppression has been shown to be important, the degree of cognitive impairment may affect drug adherence²³. If patients don't take their ART; they cannot achieve virologic suppression resulting having HAND; and because of this they can forget to take their ART. This results in a vicious circle. Therefore, it is very important to start treatment earlier and to ensure drug adherence.

Studies conducted with MoCA test in HIV-positive patients have reported that this test was promising for the early detection of cognitive functions and in long-term clinical follow-up²⁴. In a study in which MoCA test was used for the diagnosis of HAND in HIV-positive patients over 60 years old, the test's sensitivity and specificity was found as 72% and 67%, respectively²⁵. The sensitivity and specificity of the test may vary depending on the cut-off value determined for the test. Overton et al. Reported a prevalence of HAND of 64% by using MoCA in 119 HIV-infected individuals. MoCA had a sensitivity of 59% and a specificity of 81% by using a cut off point as <26; and the sensitivity increased to 83% if the cut-off point was taken as <27²⁶. Optimal cut-offs for MoCA test vary by race, education, and ethnicity. In a study conducted in Malaysia, demographically corrected MoCA scores were used to determine the prevalence of HAND, and demographically corrected rates were in agreement with international HAND prevalence rates in treated and virally suppressed HIV-positive populations²⁷. In our study, we used the Turkish version of MoCA test, which was validated for Turkey, and determined the cut off value of the test as 21, which is commended value for our country⁷.

The limitations of our study were the small number of patients and the effect of educational status on MoCA test.

Conclusion

Today, together with the increasing HIV-infected patient population, other comorbidities brought by the disease also pose an important problem. HIV-related cognitive disorders are one of them. The disease may progress asymptomatic or cause a significant deterioration in daily life activities and progress to dementia. Clinical suspicion is important in diagnosis. Although the gold standard tests for diagnosis are neuropsychological tests, alternative searches have been sought because they are difficult to apply in clinical practice, needed to be performed by experts, and take a lot of time. MoCA test are recommended as an alternative for screening and follow-up purposes in HIV-infected patients because it is sensitive to mild cognitive impairment, and it is able to monitor the cognitive functions that are frequently affected by HIV. Our study supports that MoCA test, which is highly sensitive and offers a practical approach to assessment of cognitive functions, can be used for monitoring cognitive functions in patients receiving treatment. Evaluating patients' cognitive functions before the treatment is important for the treatment selection and clinical follow-up. In our study, the rate of cognitive dysfunction was found to be 27.5% with MoCA test in treatment naïve patients. Decreasing of this rate to 7.5% after treatment supports that ARTs provide improvement in cognitive functions, which is in line with the literature. Early initiation of appropriate ART seems to be the best solution in the prevention and treatment of cognitive dysfunctions.

Declarations

Acknowledgments

I would like to express my very great appreciation to Dr. Faruk Karakeçili for his valuable and constructive suggestions for this research work. I am also grateful to Dr. Umut Devrim Binay, Dr. Orçun Barkay and Aydın Dikici for their helpful advice and guidance. And special thanks to my dear husband Dr. Mustafa Gül for always supporting me.

All listed authors meet the ICMJE criteria. We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

The study has no funding and none of the authors has any potential conflicts of interest.

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Tables

Table 1. Relationship between HIV RNA level and MoCA score

	HIV RNA (copies / ml)				p
	≤10 ⁴		>10 ⁴		
	mean.±SE	Median (Min.- Max.)	mean.±SE	Median (Min.- Max.)	
MoCA	23,39±3,46	25 (15-28)	21,59±4,24	22(10-28)	0,113
Visual spatial / executive functions	3,78±1,09	4 (1-5)	3,71±1,49	4 (0-5)	0,853
Naming	2,74±0,45	3 (2-3)	2,82±0,39	3 (2-3)	0,533
Attention	4,91±1,28	5 (2-6)	4,06±1,2	4 (2-6)	0,028
Language	2±1,13	2 (0-3)	2,12±0,93	2 (0-3)	0,884
Absraction	1,3±0,82	2 (0-2)	1,06±0,83	1 (0-2)	0,332
Delayed recall	2,7±0,97	3 (0-4)	2±1,32	2 (0-4)	0,067
Orientation	5,91±0,29	6 (5-6)	6±0	6 (6-6)	0,218

SE; standard error

Table 2. Relationship between CD4 T lymphocyte level and MoCA score

	CD4 T lymphocyte level (cell/uL)				p
	<500		>500		
	mean±SE	Median (Min.-Max.)	Mean±SE	Median (Min.-Max.)	
MoCA	22,26±3,38	22 (15-28)	22,95±4,32	25 (10-28)	0,211
Visual spatial / executive functions	4,11±0,88 (3-5)	4	3,43±1,47	4 (0-5)	0,167
Naming	2,79±0,42	3 (2-3)	2,76±0,44	3 (2-3)	0,911
Attention	4,37±1,16	4 (2-6)	4,71±1,42	5 (2-6)	0,048
Language	1,84±1,12	2 (0-3)	2,24±0,94	3 (0-3)	0,157
Absraction	1,05±0,78	1 (0-2)	1,33±0,86	2 (0-2)	0,554
Delayed recall	2,11±1,24	2 (0-4)	2,67±1,06	3 (0-4)	0,099
Orientation	5,95±0,23	6 (5-6)	5,95±0,22	6 (5-6)	0,761

SE; standard error

Table 3.The change in the MoCA scores of the patients in six months interval

	Min-Max	Median	Avg.±s.e	p
<i>Total MOCA</i>				
Initial	10,0 - 28	23,0	22,6 ± 3,9	0,001 w
Control	20,0 - 30	27,0	26,3 ± 2,6	
<i>Visual Spatial / Executive Functions</i>				
Initial	0,0 - 5	4,0	3,8 ± 1,3	0,001 w
Control	3,0 - 6	5,0	4,5 ± 0,7	
<i>Naming</i>				
Initial	2,0 - 3	3,0	2,8 ± 0,4	0,007 w
Control	2,0 - 5	3,0	3,0 ± 0,4	
<i>Attention</i>				
Initial	2,0 - 6	5,0	4,6 ± 1,3	0,001 w
Control l	3,0 - 6	6,0	5,4 ± 0,8	
<i>Language</i>				
Initial	0,0 - 3	2,0	2,1 ± 1,0	0,003 w
Control	1,0 - 3	3,0	2,5 ± 0,6	
<i>Abstract Thinking</i>				
Initial	0,0 - 2	1,0	1,2 ± 0,8	0,003 w
Control	0,0 - 2	2,0	1,5 ± 0,7	
<i>Gecikmeli Hatırlama</i>				
Initial	0,0 - 4	2,0	2,4 ± 1,2	0,001 w
Control	1,0 - 5	4,0	3,7 ± 1,0	
<i>Yönelim</i>				
Initial	5,0 - 6	6,0	6,0 ± 0,2	0,317 w
Control	5,0 - 6	6,0	6,0 ± 0,2	

^w: Wilcoxon test Avg:Average S.e:Standart Error

Figures

Figure 1: Before-After cART Scores by Education Status

Figure 1

Before-After cART Scores by Education Status

Figure 2: Before-After cART Scores by Virologic Suppression Status

Figure 2

Before-After cART Scores by Virologic Suppression Status