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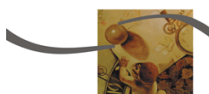
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## Mini mental state examination and evaluation of factors associated with cognitive decline in HIV/AIDS-infected people

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**ABSTRACT.** Neuropsychiatric complications are present in almost one third of patients diagnosed with AIDS who show wide variations in their clinical symptoms, featuring a spectrum of disorders ranging from minor cognitive-motor impairments to profound dementia. The Mini Mental State Examination (MMSE) is one of the most used and studied cognitive tests around the world and evaluates cognitive function and screening of dementia. Current experiment applies the MMSE to HIV/AIDS patients to screen possible dementia factors in the sample and to evaluate the association of scores that are positively associated with the emergence of cognitive impairment and possible dementia. The study population consisted of 100 HIV/AIDS patients attended at the 15<sup>th</sup> and 17<sup>th</sup> Regional Health Centers covering 50 municipalities in the northwestern region of the state of Paraná, Brazil. Whereas patients were classified with cognitive impairment and patients without cognitive impairment, the factors assessed included depression, body mass index, haematocrit, hemoglobin levels, rate of lymphocytes T CD4+, viral load and gender. Twenty-seven (27%) patients had scores lower than expected and were considered cognitively impaired. There was a significant positive association between cognitive impairment and changes in blood hemoglobin and haematocrit, age and depression.

**Keywords:** HIV/AIDS, MMSE, cognition, neuropsychological tests.

## Minixame do estado mental e avaliação de fatores que se associam à presença de declínio cognitivo em pessoas vivendo com HIV/AIDS

**RESUMO.** Complicações neuropsiquiátricas estão presentes em quase um terço dos pacientes com diagnóstico de AIDS e apresentam grande variação na sua evolução clínica, exibindo um espectro de sintomas que vai de disfunções cognitivo-motoras leves a demência profunda. O Minixame do Estado Mental (MEEM) é um dos testes mais empregados e mais estudados em todo o mundo, e permite a avaliação da função cognitiva e o rastreamento de quadros demenciais. O objetivo deste trabalho foi aplicar o MEEM em pacientes portadores de HIV/AIDS de modo a rastrear possíveis quadros demenciais na amostra, bem como avaliar a associação desses escores com os fatores carga viral plasmática maior que 50000 cópias mL<sup>-1</sup>, concentração de hemoglobina menos de 15 mg dl<sup>-1</sup>, níveis de linfócitos CD4 inferiores a 200 células mL<sup>-1</sup>, baixo índice de massa corpórea, baixo hematócrito, idade avançada, sexo feminino e depressão. A população estudada constituiu-se de 100 pacientes com HIV/AIDS atendidos na 15 e na 17ª Regional de Saúde, abrangendo 50 municípios da Região Noroeste do Paraná, classificados em pacientes com comprometimento cognitivo e pacientes sem comprometimento cognitivo mediante a aplicação do MEEM. Foram avaliados os fatores depressão, índice de massa corporal, hematócrito, níveis de hemoglobina, taxa de linfócitos T CD4+, carga viral, idade e gênero. Do total de pacientes, 27 (27%) apresentaram escores inferiores ao esperado e foram, por isso, considerados cognitivamente comprometidos. Verificou-se uma significativa associação positiva entre comprometimento cognitivo e níveis sanguíneos abaixo dos valores de referência para a hemoglobina e o hematócrito, assim como para idade avançada e depressão.

**Palavras-chave:** HIV/AIDS, MEEM, cognição, testes neuropsicológicos.

### Introduction

HIV infection in the host may produce different neurological problems which range from a mild cognitive and motor impairment, called Cognitive Motor Complex, attached to HIV (CMCHIV) and clinically manifested by a decrease in motor and

cognitive abilities of the patient. They neither significantly compromise the activities of the patient's daily life nor are sufficient to fulfill the criteria of dementia (SHAND, CARCAMO, 2002), until a more serious illness, HIV-associated dementia (HAD) which seriously affects the

activities of the patient's daily life, occurs (AAN, 1991; LÓPEZ, BECKER, 2002).

HAD is a disabling sub-cortical type of dementia of uncertain basis. Monocytes and microglial cells probably play a key role in its development whilst genetic factors may be relevant in the pathology (SZAJERKA et al., 2006). As a rule, HAD is usually rare among older patients and more common in young ones (BALLONE, 2003). However, it is the most common, avoidable and treatable neurocognitive impairment in less than 50-year-old individuals (ALMEIDA et al., 2006). It is estimated that one third of HIV-infected adults develop dementia (BALLONE, 2003) and up to 10% of asymptomatic HIV-infected persons may have dementia as an initial manifestation of HIV infection (COLOMBRINI et al., 2001).

HAD is manifested by a variety of cognitive, behavioral, affective, motor and psychiatric disorders caused by HIV infection (GHAFOURI et al., 2006). Tropism of the virus by frontal and subcortical areas may explain the attention and memory deficits, the difficulty in performing complex mental tasks and delay in mental information processing observed in these patients (BRASIL, 2004; SHAND, CARCAMO, 2002).

In studies on hypertension, some factors were positively associated with the emergence of cognitive deficits and dementia, such as high plasma viral load ( $> 50,000$  copies  $\text{mL}^{-1}$ ), low hemoglobin concentration levels ( $< 15$  mg  $\text{dL}^{-1}$ ) (ALMEIDA et al., 2006), levels of CD4 lymphocytes  $< 200$  cells  $\text{mL}^{-1}$ , low body mass index (McARTHUR et al., 2003), low haematocrit rates, a history of clinical HIV-related symptoms, old age, female gender (women have a more rapid progression of neurological signs and symptoms), intravenous drug use, race (non-Caucasian) and depression (STERN et al., 2001).

Mini Mental State Examination (MMSE), developed by Folstein et al. (1975), is one of the most widely neuropsychological tests used and studied worldwide. The test, which may be employed alone or combined with more comprehensive instruments, provides the assessment of the cognitive function and the screening of dementia (ALMEIDA, 1998; ANTHONY et al., 1982; APA, 1987; BRUCKI et al., 2003; LAKS et al., 2003), and has been used in clinical settings to detect cognitive impairment, to follow up dementia and to monitor response to treatment.

MMSE has been used in population studies and in the evaluation of responses to drug experimentation. It is also comprised in several batteries of neuropsychological tests, such as the

Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (MORRIS et al., 1989), the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX-R) (ROTH et al., 1999) and the Structured Interview for the Diagnosis of Dementia (SIDAM) (ZAUDING et al., 1991). In Brazil MMSE received the attention of clinicians and researchers and is used in clinical practice and scientific research (BERTOLUCCI et al., 1994; BRUCKI et al., 2003).

Current study applies MMSE in HIV/AIDS patients to track possible dementia in the sample and to evaluate the association of these scores with the factors viral plasma load  $> 50,000$  copies  $\text{mL}^{-1}$ , hemoglobin concentration  $< 15$  mg  $\text{dL}^{-1}$ , levels of CD4 lymphocytes  $< 200$  cells  $\text{mL}^{-1}$ , low body mass index, low haematocrit rates, age, female gender and depression.

## Material and methods

The population under analysis consisted of HIV/AIDS patients attended at the 15<sup>th</sup> Regional Health Center in Maringá and at the 17<sup>th</sup> Regional Health center in Londrina, which comprise 50 municipalities in the northwestern region of the state of Paraná, Brazil. Convenience sample consisted of selected patients who were invited to participate in current research after they had received explanations at the STD/AIDS nuclei of Maringá and Londrina. Participants signed the form of consent to participate in the study approved by the Ethics Committee on Research involving Human Beings of the State University of Maringá.

Social and economic data were collected by a closed questionnaire which included age, duration of infection, family income, education, use of alcohol/illegal drugs, use of antiretroviral drugs and the occurrence of opportunistic infections. MMSE was used in the original version, proposed by Bertolucci et al. (1994), for cognitive screening.

Hamilton (1959), retrieved from the *Guide to the Use of Assessment Tools: Detecting Depression (and Anxiety) in the Elderly Patient*, was used to evaluate and measure depression. Hamilton Scale covers items related to depressed mood, guilt, suicide, insomnia (initial, intermediate, late), work and other activities, retardation, agitation, anxiety (psychic, somatic, gastrointestinal), general somatic symptoms, hypochondria, loss of weight, awareness, depersonalization, loss of reality and paranoid symptoms, obsessive and compulsive symptoms. Each item is scored according to Likert scale, ranging from zero to four, and interpreted as a total score: score 8 to 13 indicates mild depression; 14 to 18, moderate depression; 19 to 22, severe depression; over 23, very severe depression.

Montgomery and Asberg depression scale (MADRS) was applied as a confirmatory test, with scores for each item, ranging between zero and six (one, three and five were intermediate values). Total score from 13 to 24 indicated mild depression; from 25 to 30, moderate depression; from 31 to 43, a worsening depression; score over 44 indicated very severe depression (ADLER et al., 2008).

Each instrument was administered by a single evaluator, which ensured uniformity in contact and in data collection. The interviews, with an average duration of twenty minutes, were individual and agreed to on a previously prepared schedule. Analyses were performed according to the standardization and validation of each instrument.

The calculation of body mass index was carried out by  $BMI = \text{Weight} / \text{Height}^2$ . Measures of body weight were performed using a Welmy lever balance with a 100 g precision. For the above measuring, the patient, barefoot and with as little clothing as possible, was requested to stay at the center of scale platform and remain upright with arms at his sides and looking ahead so that no oscillations would occur at the registration of the measure. The balance was calibrated before the start of weighing and at every other ten weighings. Height was measured in cm using an inelastic tape, with the patient in an upright position, with his arms at his sides and looking straight ahead.

Hematologic parameters (haematocrit and hemoglobin concentration) were determined by automated cell counter MINDRAY BC-3000 Plus and by microscopic evaluation.

The levels of T CD4+ lymphocytes and viral load were obtained from data of the reports on the patients' charts.

Statistical comparisons were made between patients with cognitive impairment and those without impairment cognitive, using STATISTICA 8.0, by frequency analysis followed by Mann-Whitney test, with statistically significant rates at  $p < 0.05$ .

## Results and discussion

One hundred patients out of 2,000 patients (1,320 and 680 respectively from the Regional Units of Maringá and Londrina municipalities) who were at the Health Unit on the investigation days and were willing to participate were evaluated. They became the population sample in current study. In fact, 59 (59%) and 41 (41%) were from the 15 and 17<sup>th</sup> Regional Health Units, respectively of Maringá and Londrina. Within the total, 62 (62%) were males and 38 (38%) females. Table 1 shows the demographic data. Females' age bracket ranged

between 26 and 64 years (mean 42 years) and males' age bracket between 20 and 56 (mean 40 years).

With regards to schooling, 75% had primary education and 23% had secondary education, whilst 2% had no schooling at all. Lowest schooling was observed among females.

All patients received antiretroviral therapy for a period of two to ten years, with an average of seven years.

**Table 1.** Frequency distribution of the study population according to social demographic characteristics of HIV/AIDS patients with cognitive impairment (CI) and without cognitive impairment (WCI) by MMSE.

Characteristics	CI (n = 27)		WCI (n = 73)	
	n	%	n	%
Sex				
Male	17	63	45	64
Female	10	37	28	38
Age				
< 50 years	21	77	63	86
> 50 years	6	23	10	14
Education				
Elementary	18	67	57	78
Secondary	7	26	16	22
No schooling	2	7.4	0	0

Further, 27 (27%) of total patients had a lower score than expected on the MMSE scale at the cutoff point following Dr. Paulo Henrique Ferreira Bertolucci (EPM/Unifesp). Since patients were divided into two groups, results show that mean  $\pm$  SD of CI patients' total MMSE score was  $20.5 \pm 1.95$ , whereas WCI patients' score reached  $27.7 \pm 1.69$ .

Table 2 shows data on BMI, haematocrit, hemoglobin levels, rate of T CD4+ lymphocytes and viral load. Changes were considered statistically significant for the parameters haematocrit, low hemoglobin levels and age > 50 years.

**Table 2.** Clinical and laboratory parameters in HIV/AIDS patients with cognitive impairment (CI) and without cognitive impairment (WCI) by MMSE.

Evaluated clinical and laboratory parameters	CI (n = 27)		WCI (n = 73)	
	n	%	n	%
BMI < 18.5	0	0	4	5.4
Haematocrit < 36% (female); < 40% (male)	9*	33*	10	13.7
Hemoglobin levels < 12 g dL <sup>-1</sup> female); 13 g dL <sup>-1</sup> (male)	32.7 $\pm$ 0.7	33*	40.2 $\pm$ 0.3	13.7
Rate CD4+ lymphocytes < 200 cells mm <sup>-3</sup>	5	18.5	23	31.5
Viral load > 50,000 copias mL <sup>-1</sup>	358.5 $\pm$ 29	11	390 $\pm$ 26.8	11
Age > 50 years	3	11	8	11
Females	6*	22*	10	13.7
	46.41 $\pm$ 1.9		36.3 $\pm$ 0.8	
	10	37	28	38

\*p < 0.001.

As to the variable depression (Table 3), significant differences were observed between the groups, although the results of the two scales coincided. The CI group had a higher incidence of moderate depression while a higher incidence of mild depression occurred in the WCI group.

**Table 3.** Levels of depression in HIV/AIDS patients with cognitive impairment (CI) and without cognitive impairment (WCI) by the MMSE.

Levels of depression	CI (n = 27)		WCI (n = 73)	
	n	%	n	%
Absent	6	22	15	20
Light	2*	7.4*	16	22
Moderate	12*	44*	25	34
Serious	7	26	17	24

\*p < 0.001.

Current study evaluated the presence of cognitive impairment by MMSE used as a screening instrument and related these results to factors associated with the presence of a positive cognitive impairment in patients with HIV/AIDS patients on antiretroviral therapy.

The introduction of Highly Active Antiretroviral Therapy (HAART) has improved cognitive performance and decreased incidence of HIV-associated dementia. Many of the cognitive deficits, even in cases of dementia, were stabilized or regressed, partially or completely, with antiretroviral therapy. This has been attributed to the recovery of the immune status, as evidenced by an increase in CD4 lymphocytes, the reduction in viral load or antiretroviral direct effect on tCNS (McARTHUR et al., 2003).

Before the introduction of HAART, almost 30% of the infected population developed HAD at a later stage with AIDS. With the use of HAART the rate was reduced to 10% (GHAFOURI et al., 2006). In general, the severity of dementia in the post-HAART era has diminished and a mild form of cognitive dysfunction, called Minor Cognitive Motor Disorder (MCMD), is now the most common form of cognitive dysfunction in HIV-infected patients (BANDARU et al., 2007). Cognitive symptoms, neurological and psychiatric disorders are subtle and functional complaints are minimal under these conditions. However, in some cases, cognitive deficits and MCMD are related to later onset of dementia (FOLSTEIN et al., 1975).

Current results show a 27% incidence of cognitive impairment when MMSE is applied to patients with at least two years of HAART. These data may still be considered merely indicative, with a higher incidence of cognitive disorders in HIV-infected populations than in the elderly (LAKS et al., 2003). Moreover, result is similar to the incidence of MCMD before the introduction of HAART.

Post-HAART reports indicate a decreased incidence of HAD, although the incidence of HIV-associated encephalitis identified on postmortem exams has not changed (VALCOUR et al., 2004). HAD's epidemiological aspect highly oscillated

owing to changes in diagnostic criteria (SZAJERKA et al., 2006). Postmortem studies evidenced damage to the CNS in about 80% to 90% of HIV-infected patients (LÓPEZ; BECKER, 2002).

Studies by Valcour et al. (2004) in a group of 202 HIV positive patients showed an overall 36% rate of MCMD, slightly higher than the rates found in other studies in HIV positive populations in the post-HAART era. Current studies corroborate the above findings.

With regard to the factors associated with cognitive disorders in current study, there was a significant association between changes in laboratory hematology parameters (hemoglobin and haematocrit) and evidenced that a lower hemoglobin and haematocrit blood rate is related to MMSE-diagnosed cognitive changes.

Current study that a viral load greater than 50,000 copies mm<sup>-3</sup> and a CD4+lymphocyte rate lower than 200 cells mm<sup>-3</sup> showed no correlation with values which might indicate MMSE diagnosed-cognitive impairment. This result could be attributed to the antiretroviral treatment used by all patients in current study, which would be keeping low the blood viral load. With regard to CD4+ lymphocytes levels, it is currently known that a percentage of patients do not recover within this immunological parameter even with antiretroviral treatment. However, their clinical condition does not deteriorate; others experience a quantitative recovery of CD4+ lymphocytes albeit with a deficient quality of immune response.

There was a significant correlation in the group evaluated between the age of 50 years and cognitive impairment when the parameters body mass, age and gender were taken into account. Results, consistent with studies with HIV-negative populations, demonstrate that age is the most significant social and demographic variable (DINIZ et al., 2007; LAKS et al., 2003).

Albeit low in the sample population, schooling is another factor present in studies that demonstrate that people with low schooling had a better performance in cognitive tests when compared to those with no schooling (DINIZ et al., 2007).

Current study shows the significant relationship between the level of depression and cognitive impairment. HIV-infected individuals with cognitive impairment had more severe degrees of depression than patients without cognitive impairment (Table 3). Depression is the condition that generates higher diagnostic confusion with dementia. Since depression is a potentially treatable condition, the distinction between the two conditions is mandatory. Both depression and dementia cause mental retardation,

apathy, irritability, personal carelessness, difficulties in concentration and memory, and changes in behavior and personality. Depression may also be a symptom of dementia and often both situations coexist (GALLUCCI-NETO et al., 2005; RASKID, 1998), as may be seen even in current analysis.

## Conclusion

Although the incidence of HIV-associated dementia has decreased with HAART, the incidence of HIV-associated dementia has actually increased from 6.6 per 100 persons in 1994 to 10 in 2000, or rather, an increase in survival which reinforces the need to develop sensitive and valid predictive markers for HIV-associated dementia.

Our results indicate an effective implementation of the functionality of MMSE in the perception of cognitive impairment in HIV/AIDS-patients. With regard to cognitive impairment associated with the factors studied, it may be said that there is a significant association among biochemical alterations in blood levels of hemoglobin and haematocrit, age and depression.

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