NEUROCOGNITIVE PERFORMANCE IN PATIENTS WITH AIDS IN BRAZIL: A CASE-CONTROL STUDY

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Abstract

Objective: The objective of the present study was to evaluate the different cognitive domains in a sample of patients with AIDS, taking as a comparison group participants without known HIV infection or AIDS, seen at a referral outpatient facility that provides care to HIV patients in Minas Gerais, Brazil.

Method: A total of 110 subjects with AIDS followed up at the Infectious Diseases Outpatient Clinic were studied. The subjects were submitted to neurological and neuropsychological evaluation. Neuropsychological tests were used for the evaluation of cognitive skills; processing speed, working memory, attention, executive function, learning and memory, language and verbal fluency, fine motor abilities and e visuospatial abilities.

Results: The comparison of cognitive performance between cases and controls showed significantly statistical differences in all tests employed. The AIDS subjects consistently presenting a worst performance.

Conclusions: The results presented herein suggest that subjects with AIDS, independently of their immune status and antiretroviral treatment have worse neurocognitive performance in all domains studied in relation the control group.

Key words: HIV, executive function, memory

Declaration of interest: none

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Introduction

The central nervous system (CNS) is an important target of the human immunodeficiency virus (HIV) since the virus is neurotropic and, in the presence of an intact blood-brain barrier, there is poor penetration of antiretroviral drugs. The CNS is a sanctuary for HIV1. Autopsy studies of HIV-positive patients demonstrated the presence of the virus in cortical and subcortical structures, such as the frontal lobes, subcortical white matter and basal ganglia (Navia et al. 1986). These findings have been supported by structural neuroimaging studies that emphasize the existence of alterations in white matter and fronto-striato-thalamic circuits in patients infected with HIV (Aylward et al. 1993). Chronic HIV-1 infection can result in neurodegenerative disease, overall termed NeuroAids. The expression of this process includes neurocognitive impairments en several domains (Shapshak et al. 2011).

The diffuse nature of HIV-associated neuropathology creates notable challenges in directly translating such non-specific neurobiological mechanisms of HIV into testable hypotheses for studies of cognitive neuropsychology, but early observations that the neurobehavioral profile of HIV-Associated Neurocognitive Disorders (HAND) was most consistent with that of other 'subcortical' disorders (e.g., Huntington's disease), with deficits especially in the areas of motor skills, processing speed, and executive functions. Beside these, information processing, learning and memory, attention and working memory, visuoperception, speech and language have been frequently associated with HAND (Woods et al. 2009).

In Brazil, 506,000 cases of AIDS have been reported since the identification of the first case in 1982 until June 2008. It is estimated that approximately 630,000 people currently live with HIV or AIDS. According to World Health Organization data, the prevalence of HIV infection in Brazil is 0.61% in the population aged 15 to 49 years, with prevalence of 0.42% among women and of 0.80% among men (Christo 2010).

The Brazilian public health system provides antiretroviral drugs free of charge to patients with AIDS which makes the studies of HAND in this population important since Brazil is an emerging nation and the people have characteristics which are different from those in industrialized or underdeveloped countries.

In view of the importance of cognitive functions for productivity and performance of daily activities, the objective of the present study was to evaluate

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the impairment of evaluate the different cognitive domains in a sample of patients with AIDS, taking as a comparison group participants without known HIV infection or AIDS, seen at a referral outpatient facility that provides care to HIV patients in the state of Minas Gerais, Brazil.

Subjects and methods

A total of 110 subjects with AIDS (cases) followed up at the Public Infectious Diseases Outpatient Clinic of Hospital Eduardo de Menezes, Belo Horizonte, Minas Gerais, Brazil, were studied. The subjects were recruited during their routine visit to the infectious disease specialist and were submitted to neurological and neuropsychological evaluation.

The study was approved by the Research Ethics Committee of the Institution and written informed consent was obtained from all participants. The subjects had no current history of diffuse or focal CNS disease, head trauma, systemic disease, alcohol abuse, known psychiatric disease, or treatment with antipsychotic drugs.

Neurological evaluations were performed and the following neuropsychological tests were used for the evaluation of cognitive skills: selective attention and processing speed (Stroop task parts 1 and 26, Trail-making test part A7, and digit span and coding subtest of the Wechsler Adult Intelligence Scale - WAIS III (Wechsler 1991); language: phonemic verbal fluency - FAS test (Gladsjo et al. 1999) and semantic verbal fluency (animal categories); non-verbal fluency (total number of drawings in the 5-point test (Regard et al. 1982); cognitive flexibility (trail-making test part B); inhibitory control (Stroop task part 3); phonological loop of working memory (digit symbol subtest of the WAIS-III, direct repetition), and central executive working memory (digit symbol subtest of the WAIS-III,). Learning and memory - Rey Auditory Verbal Learning Test – *RAVLT* (Malloy-Diniz LF et al. 2009) and Rey Complex Figure (Jamus and Mader 2005), fine motor coordination - Nine Hole Peg Test (Rodrigues et al. 2005) and visuospatial abilities (Rey Complex Figure).

The comparison (control) group was selected among relatives and participants accompanying the patients seen at the outpatient clinic of Hospital Eduardo de Menezes, as well as among employees of the hospital. Criteria for inclusion in the control group were age older than 18 years and being literate. Patients with a history of neurological disorders such as stroke and epilepsy, cognitive impairment identified by a lower score than expected for age/educational level in the Mini-Mental State Examination (Bertolucci et al. 1994), presence of depressive symptoms identified by interview using the Beck Depression Scale (a score>12 indicates signs and symptoms of depression), and treatment with antidepressants, neuroleptics, anticonvulsant and mood-stabilizing agents were not included in the study. Those who fulfilled the inclusion criteria were also asked to sign the free informed consent form to be admitted in this investigation.

Statistical analysis

Statistical analysis comparing means or proportions between cases and controls was performed using T-test and chi-square. A p-value of .05 was used to define a significant difference. For effect size we used Cohen's d. The STATA 10.0 software was used to analyze the data.

To identify a worse neurocognitive performance, we used a statistical difference (p value below 0.05) and clinically relevant effect size (more than 0.3).

Results

Demographic characteristics of cases and controls included in the study are shown in **table 1**. Age distribution was similar comparing cases and controls; controls have more years of education compared to cases. Regarding gender, a higher proportion of males were observed among cases.

The cases laboratory data (time since diagnosis, mean CD4 count, mean viral load) are summarized in **table 2**. Among the 110 subjects studied, 21% had a past history of opportunistic neurological disease (toxoplasmic encephalitis, cryptococcal meningitis, and tuberculous meningitis) and 62% used HAART.

The comparison of cognitive performance between cases and controls, in terms of attention skills, inhibitory control, verbal fluency (animal category verbal fluency test and phonemic FAS fluency test), non-verbal fluency (5-point test), and working memory and concentration (digit span subtests of the WAIS-III) Learning and memory (Rey Auditory Verbal Learning Test - RAVLT and Rey Complex Figure) fine motor coordination (Nine Hole Peg Test) and visuospatial abilities (Rey Complex Figure) is depicted in **table 3**. Significantly statistical differences were observed in all tests employed, cases consistently presenting a worst performance.

Table 1. *Demographic characteristics of cases and controls*

	HIV(n=110)	Controls (n=64)	p-value
Age in years, mean(sd)	43.5 (9.4	41.3 ± 14.8	0.23
Education in years, mean (sd)*	6.6 (3.2	8.0 ± 3.5	0.008
Gender *			
Female	35 (31.8%)	41 (64.0%)	0.001
Male	75 (68.2%)	23 (35.9%)	

* p<0.05, statistically significant differences

Discussion

In Brazil there are insufficient data on the neurocognitive effects of HIV. These studies are important, since despite of the social-cultural level is lower than in developed countries, the HIV patient in Brazil has access to antiretorviral treatment free of charge. There are few Brazilian studies of cognitive assessment in patients with AIDS, but this is the first to evaluate a large number of patients and various cognitive domains.

The studied cohort presented alterations in all neuropsychological tests when compared to the

Table 2. *Laboratory characteristics of the studied patients with AIDS*

	Mean	sd	Minimum	Maximum	Median
Time since diagnosis (months)	72.8	45.3	3.0	192.0	72.0
CD4 count (initial)	313.8	285.2	12.0	1,690.0	223.0
CD4 count (last 3 months)	487.2	224.2	52.0	974.0	452.0
Viral load (log) (initial)	4.0	1.2	1.1	5.9	4.4
Viral load (log) (last 3 months)	2.6	1.2	0.9	5.4	1.7

sd: standard deviation

Table 3. *Neurocognitive performance in HIV and Controls subjects*

	HIV				CONTROL					
	Mean	Median	SD	Min-Max	Mean	Median	SD	Min-Max	p-value	Cohen's D
V.F.A.	13,51	13,5	4,39	5-24	14,94	14	4,58	5-27	0,08	0,32
V.F.f.a.s*	29,21	30	11,23	2-56	35,38	33	11,56	15-75	0,001	0,54
5P*	11,21	9,5	7,48	1-37	22,06	23,5	9,45	5-43	0,001	1,28
Stroop A*	24,58	20	12,59	11-75	19,28	17	7,82	12-50	0,001	0,52
Stroop B*	29,73	26	13,91	14-85	21,69	19,5	6,94	14-40	0,001	0,77
Stroop C*	45,27	38	29,36	13-210	34,84	33	11,44	18-70	0,02	0,51
Digit Span*	11,81	12	3,16	5-21	14,33	14	4,22	7-24	0,001	0,68
Coding*	34,64	31	17,25	2-91	51,11	51,5	23,25	7-148	0,001	0,81
TMT- A*	87,18	73	58,24	11-300	59,73	52,5	31,26	20-218	0,001	0,61
TMT- B*	214,87	180	105,18	57-600	139,16	118	81,26	25-420	0,001	0,81
RAVLT- Tot*	40,22	40	9,14	17-61	43,3	44	9,4	24-62	0,05	0,33
RAVLT- Rec*	13,07	14	2,4	5-15	12,21	13	3,05	3-15	0,03	0,32
RCF- 1*	23,43	24,5	10,41	2-36	29,92	32	7,82	8-36	0,001	0,71
RCF- 2*	9,84	8	7,8	1-34	14,74	15	8,87	1-32	0,001	0,59
RCF-3*	9,69	8	7,58	1-34	14,44	14	8,58	2-32	0,001	0,59
9HP*	21,79	20,5	4,79	15,5-49,5	20,09	20	2,95	16-32	0,01	0,44

* $p<0.05$, statistically significant differences

sd: standard deviation; min: minimum value ; max: maximum value; V.F.A.: verbal fluency animals; V.F.f.a.s. : verbal fluency f.a.s.; 5P: 5-points test; Stroop A-B-C: Stroop test, parts A, B and C.; Digit Span: digit span from WAIS-III; Coding: Coding from WAIS-III; TMT-A and B: trail-making test parts A and B; RAVLT-Tot: Rey Auditory Verbal Learning Test A1 to A5; RAVLT-Rec: Rey Auditory Verbal Learning Test recognition score -15; RCF-1,2 and 3: Rey Complex Figure parts 1, 2 and 3; 9HP: Nine Hole Peg Test.

control group, with the observation of impairment of all evaluate functions such as attention, concentration, inhibitory control, working memory, mental flexibility, planning, fluency, processing speed, working memory and attention, learning and memory, language, fine motor coordination and visuospatial abilities. These altered functions were observed despite the use of antiretroviral drugs by most patients and reasonable immunity. When we analyse the clinical impact of this differences, showed in effect size analyses, we found a large impact in cognitive performance, especially in executive functions tasks, tipicaly found in subcortical dementias (Christo 2010).

As has been described (Woods et al. 2009), the neurocognitive pattern of HIV patients showed diffused damage with a worse performance on neuropsychological tests compared to the control group. This worse performance appeared in all the tasks given, suggesting that this affects many cognitive domains and, consequently, the functioning of various cerebral structures.

Deficits in executive functions are associated with impairments in everyday functioning affecting the quality of life of AIDS patients, as well as of their relatives (Heaton et al. 2004). Prospective memory deficits provides incremental ecological in predicting general IADL declines and medication mismanagement (Woods et al. 2009).

The results presented herein suggest that subjects with AIDS, independently of their immune status and antiretroviral treatment have diffuse impaired neuropsychological functions. Further studies are needed to better understand the clinical and neurocognitive evolution of patients with AIDS and HIV infection in Brazil, and to propose interventions that help patients to identify and monitor their cognitive deficits. Thus improving their quality of life and infection control. Endeavors to establish a more standardized approach to neurocognitive assessments across local studies in addition to more accurate rating of neuropsychological test performance will be important and necessary to our country.

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