UNIVERSIDADE FEDERAL DE MINAS GERAIS

LUCAS ARAÚJO LIMA GÉO

FREQUÊNCIA, CORRELATOS E PERFIL NEUROPSICOLÓGICO DO TRANSTORNO DA COGNIÇÃO ASSOCIADO COM A INFECÇÃO PELO HIV

BELO HORIZONTE

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Dissertação apresentada ao Curso de Mestrado do Programa de Pós-Graduação em Neurociências da Universidade Federal de Minas Gerais como requisito parcial à obtenção do título de Mestre em Neurociências.

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Para mim, ele estava sendo feito o canoeiro mestre, com o remo na mão, no atravessar o rebelo dum rio cheio. – "Carece de ter coragem... Carece de ter muita coragem..." – eu relembrei. Eu tinha.

(Riobaldo em Grande Sertão: Veredas – João Guimarães Rosa, 1956)

Resumo

GÉO, Lucas Araújo Lima. **Frequência, correlatos e perfil neuropsicológico do transtorno da cognição associado com a infecção pelo HIV**. Belo Horizonte, 2014. Dissertação (Mestrado em Neurociências)- Pós-graduação em Neurociências, Universidade Federal de Minas Gerais, 2014.

O Transtorno da Cognição Associado com a Infecção pelo HIV (*HIV-associated Neurocognitive Disorders* - HAND) é causado pela ação direta do vírus HIV no Sistema Nervoso Central (SNC) ou pela ação indireta dos processos metabólicos relacionados à infecção. O quadro pode , em sua evolução, pode levar até mesmo à demência. O HAND apresenta um padrão descrito como subcortical, ou seja, atinge estruturas cerebrais como a substância branca e os núcleos da base. Entre as dificuldades cognitivas relatadas na literatura em pacientes acometidos por HAND estão os déficits na memória episódica, havendo interesse atual em avaliar se tal comprometimento é similar ao que ocorre em outras demências, como na Doença de Alzheimer. Os objetivos do presente trabalho foram caracterizar a frequência de HAND em uma população hospitalar infectada pelo HIV, detectar correlatos clínicos e o padrão subcortical associados, além de avaliar o uso do teste de aprendizagem e memória episódica auditivo-verbal. A frequênciatotal de HAND foi de 71,8% dos pacientes HIV/SIDA. Os fatores de risco encontrados foram o diagnóstico de dislipidemia, baixo nível plasmático de hemoglobina e baixo nível educacional. Com relação à memória episódica, o padrão subcortical foi observado nos pacientes acometidos pela HAND em comparação aos pacientes com quadro neurodegenerativo, ou seja, dificuldade na estratégia de busca da informação e não de seu armazenamento.

Palavras chave: HIV, cognição, demência, fatores de risco, epidemiologia.

ABSTRACT

The HIV-associated Neurocognitive Disorders (HAND) is caused by direct action of the HIV virus in the Central Nervous System (CNS) and by indirect action of related metabolic processes associated with the infection - condition that can even drive to dementia. HAND show a pattern described as subcortical which damage white matter brain structures and basal ganglia. Impairment in episodic memory is usually describe in literature and is aim of study by many researchers since is a typical difficulty in Alzheimer's disease. The objectives of this study were characterizing the prevalence of HAND in a hospital population infected with HIV, detect the risk factors and subcortical pattern as well as evaluate the use of auditory-verbal learning test and episodic memory. The overall prevalence of HAND was 71.8% of patients infected with HIV/AIDS. The clinical correlates found were the presence of dyspilidemia, lower hemoglobin level and lower formal educational. The subcortical pattern was observed in HAND; the performance demonstrated typical pattern of impairment in information retrieval strategy but not in storage. The data showed a pattern of high prevalence, risk factors peculiar to the population studied, with subcortical damage characteristics typically described in the literature.

Key words: HIV, cognition, dementia, risk factors, epidemiology

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LISTA DE ABREVIATURAS E SIGLAS

AIDS	Síndrome da Imunodeficiência adquirida
AD	Alzheimer's Disease
ANI	Asymptomatic Neurocognitive Impairment
ART	Antiretroviral Therapy
BMI	Body Mass Index
cART	Combination Antiretroviral Therapy
CD4	Grupamento de diferenciação 4
CNS	Central Nervous System
CPE	ART Penetration-Effectiveness ranking
DA	Doença de Alzheimer
MCD	HIV-Associated Minor Cognitive Disorder
MCI	Amnestic Mild Cognitive Impairment
MND	Mild Neurocognitive Disorder
HAART	Highly Active Antiretroviral Therapy
HAD	HIV-Associated Dementia
HAND	Transtorno da Cognição Associado com a Infecção pelo HIV ou HIV-associated Neurocognitive Disorders
HCV	Hepatitis C Virus
HIV	Vírus da Imunodeficiência humana
IADLs	Instrumental Activities of Daily Living Scale
IHDS	International HIV Dementia Scale
LOT	Learning Processes in RAVLT
OMS	Organização Mundial de Saúde
RAVLT	Rey’s Auditory Verbal Learning Test
REC	Recognition Memory in RAVLT
SNC	Sistema Nervoso Central

SPSS	Statistical Package for Social Sciences
TBI	Traumatic Brain Injury
TOT	Total score in RAVLT

LISTA DE ANEXOS

SUMÁRIO

1- INTRODUÇÃO

A Síndrome da Imunodeficiência Adquirida (sida-aids) foi descrita no inicio dos anos 80 e se disseminou pelo mundo tornando-se um dos maiores desafios de saúde pública das três últimas décadas. Aids é a manifestação clínica e/ou de resultados laboratoriais que indiquem deficiência imunológica da infecção pelo vírus HIV e que leva, em média, oito a dez anos para se manifestar. A Organização Mundial de Saúde (OMS) estima que, no mundo, aproximadamente 34 milhões de pessoas estão infectadas pelo vírus HIV ou apresentam a doença e que em 2011 ocorreram 1.7 milhões de mortes e cerca de 2.5 milhões de novos casos (UNAIDS, 2012). No Brasil, desde a identificação do primeiro paciente com Aids, em 1982, até junho de 2012, já foram identificados 656.701 casos da doença. Somente em 2011, foram notificados 38.776 casos.

O transtorno da cognição associado à infecção pelo HIV é conhecido na literatura como distúrbios neurocognitivo associado ao HIV (HIV-associated neurocognitive disorders - HAND), que apreende o estágio mais severo, demencial, mas também os estágios mais sutis, como o de comprometimento cognitivo leve e comprometimento cognitivo assintomático associado ao HIV. Demência por HIV contribui para morbidade da infecção e é um fator de risco para mortalidade (Sackor et al. 1996).

É de grande importância identificar o número de pacientes com danos cognitivos, uma vez que afetam a qualidade de vida, função laborativa e aderência à medicação (McArthur, 2004, Price et al. 1999).

O termo Complexo Demência associado ao HIV refere-se à constelação de sintomas e sinais cognitivos, motores e comportamentais e é classificada como uma demência “subcortical” conforme estudos de neuroimagem e anátomo-patológicos, portanto tem alguma similaridade com a demência das doenças de Huntington e Parkinson (Sadek et al. 2004).

A avaliação neuropsicológica tem um papel chave na identificação e diagnóstico de distúrbios cognitivos associados ao HIV e é usada para quantificar alterações em processos cognitivos associado com o tratamento. Testes neuropsicológicos são sensíveis para detectar distúrbios cognitivos na infecção pelo HIV-1 e devem incluir os seguintes domínios: 1-atenção/concentração; 2-rapidez do processamento da informação; 3- função executiva; 4-raciocínio/abstração; memória/aprendizado; 5-habilidade visuoespacial; e 6-funcionamento motor.

O perfil de comprometimento cognitivo pelo HIV é tipicamente subcortical (Cohen et al. 2010), porém com uma variabilidade grande na ocorrência dos domínios afetados, o que pode gerar grande dificuldade no processo avaliativo e até mesmo dúvidas diagnósticas com outros processos demenciais, até mesmo os considerados corticais, como Doença de Alzheimer (DA) (Sadek et al. 2007). Quando se define como demência subcortical, o esperado é um comprometimento típico em velocidade do processamento de informações e ou psicomotora, presença de sintomas psiquiátricos como depressão, ansiedade e apatia, bem como alterações em funções executivas (Woods et al. 2009, Christo, Géo & Antunes, 2013). Esta alteração nas funções executivas, que tem funcionamento preponderantemente cortical, se deve a estruturas mais internas no cérebro, como os núcleos da base. Para uma avaliação neuropsicológica eficaz, é necessária uma avaliação global do desempenho cognitivo, já que todos os domínios cognitivos podem estar alterados, mesmo que em menor intensidade (Christo, Géo & Antunes, 2013).

Com o envelhecimento da população infectada pelo HIV, os riscos de HAND e confusões diagnósticas com outros processos demências associados à idade como DA, lançam num novo desafio para profissionais da saúde (Xu & Izeku, 2009), que necessitarão de novas tecnologias para diagnóstico diferencial e tratamento. A freqüência de HAND na

população brasileira ainda é pouco estudada, com resultados apontando a prevalência entre 52-65% (Rodrigues, Oliveira, Grinsztejn & Silva, 2013, de Almeida et al. 2013).

O presente estudo é dividido em duas etapas. A primeira pretende estabelecer a freqüência de HAND em uma amostra de sujeitos com AIDS a partir de uma avaliação neuropsicológica completa envolvendo diversos domínios cognitivos. Também pretende avaliar a relação entre fatores de risco/proteção e o declínio cognitivo em pacientes com AIDS. No segundo artigo compararemos os pacientes HAND com pacientes com danos cognitivos provavelmente relacionados a quadros neurodegenerativos como o Comprometimento Cognitivo Leve Amnéstico e a Doença de Alzheimer, no intuito de investigar o padrão subcortical x cortical das alterações através do desempenho em tarefa de memória episódica auditiva-verbal. Em particular, pretendemos verificar a aplicabilidade desta tarefa no auxílio à diferenciação do padrão de funcionamento subcortical x cortical de comprometimento de memória. Tal diferenciação é importante considerando-se o diagnóstico diferencial entre demências, especialmente em pacientes HAND que, devido a maior sobrevida mediante a medicação, podem desenvolver outros processos demências como Doença de Alzheimer.

2 - OBJETIVOS

2.1 Objetivo geral

-Investigar a frequência dos transtornos HAND, bem como seus fatores de risco associados e seu perfil de comprometimento neuropsicológico.

2.2 Objetivos específicos

-Verificar se o padrão epidemiológico brasileiro é semelhante aos padrões internacionais, onde geralmente são descritos em países de primeiro mundo ou de extrema pobreza, como países africanos.

-Investigar características de vulnerabilidade da população brasileira para o desfecho cognitivo comprometido, com características sociodemográficas peculiares em comparação internacional.

-Investigar se pacientes com HAND apresentam um padrão de comprometimento de memória episódica característico de demências subcorticais

-Investigar diferenças entre pacientes com HAND e Doença de Alzheimer na memória episódica (padrão subcortical x cortical).

3- FREQUENCY AND RISK FACTORS OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS IN A BRAZILIAN POPULATION

Abstract:

Background: It is estimated that in Brazil approximately 630,000 people currently live with HIV or AIDS. HIV-1 can cause several neurological disorders, collectively known as HIV-associated neurocognitive disorders. Although the incidence of dementia-HIV has dropped since the advent of HAART, it continues to be a significant cause of morbidity in infected patients. In view of the importance of cognitive functions for productivity and performance of daily activities, the objective of the present study was to evaluate the frequency of neurocognitive deficits and their risk factors in a sample of patients with AIDS seen at a referral outpatient facility that provides care to HIV patients in the state of Minas Gerais, Brazil.

Methods: The sample was composed of 110 patients with AIDS and 64 control individuals. The patients were randomly recruited during their routine visit to the infectious disease specialist and were submitted to neurological and neuropsychological evaluation. This included medical history, structured neurologic and medical examination, as well as both functional and neuropsychological assessment and the prevalence of impairment by classifying the individuals in the groups considering test performance and IADL score due Frascati criteria.

Results: According to standardized neuropsychological scores, the patients were classified into neurocognitive diagnoses; asymptomatic neurocognitive impairment was observed in 56% of patients, HIV dementia in 4,5%, HIV-associated minor cognitive disorder was observed in 11% and 28% were normal. When comparing normal and impairment groups in a univariate analysis, there are differences between them concerning age, years of education,

provenance from cities other than the capital of the state, presence of dyslipidemias and hemoglobin levels. After a multivariate analysis there were differences between them concernig years of education, dyslipidemia e hemoglobin level.
Conclusion: HAND is quite frequent in patients with HIV in Brazil with asymptomatic form, the most prevalent manifestation. The presence of dysplidemia, low hemoglobin level and low formal education were the risk factors related to HAND.

Introduction

Approximately 34 million people worldwide are infected by HIV-1 (Global Report/Unaids, 2013). In Brazil since the beginning of the epidemic in 1980 until June 2011, 656.701 cases were registered. The incidence rate in Brazil was 20,2 cases/100,000 inhabitants in 2010 (Boletim epidemiológico AIDS-DST, 2011). It is estimated that in Brazil approximately 630.000 people currently live with HIV or AIDS (Christo, 2010).

HIV-1 can cause several neurological disorders, collectively known as HIV-associated neurocognitive disorders (HAND). HAND encompass a hierarchy of progressively more severe patterns of central nervous system (CNS) involvement, ranging from asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), to the more severe HIV-associated dementia (HAD; also known AIDS dementia complex, [ADC], or HIV encephalopathy) (Antinori et al. 2007).

Although the incidence of HAD has dropped by approximately half since the advent of HAART, it continues to be a significant cause of morbidity in infected patients (McArthur, Sacktor & Selnes 1999; Sacktor, et al. 2002). Its prevalence, on the other hand, has actually increased owing to the enhanced survival of HIV-1 infected patients receiving HAART (McArthur, 2004; Selnes, 2005).

Before the widespread use of HAART in the developed world, 20%–30% of individuals infected with HIV-1 developed a range of cognitive and motor symptoms that are collectively known as HAD. It has recently been estimated that ~10% of HIV-1 infected adults have HAD but that MND might be several times more common, involving perhaps as many as 30% of the HIV-1 infected population (Brew et al. 2009). This includes individuals who are not immune suppressed as well as those with end-stage acquired immunodeficiency syndrome (AIDS) (Grant, Sacktor & McArthur, 2005).

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 the frequency of neurocognitive deficits and their risk factors in a sample of patients with AIDS seen at a referral outpatient facility that provides care to HIV patients in the state of Minas Gerais, Brazil.

Methods

Subjects:

The patients were randomly recruited during their routine visit to the infectious disease specialist and were submitted to neurological and neuropsychological evaluation. The control group was selected among relatives and persons accompanying the patients seen at the outpatient clinic. The study was approved by the Research Ethics Committee of the institution and written informed consent was obtained from all participants.

The sample was composed of 110 patients with AIDS and 64 control individuals. The group of patients was composed of individuals followed up at the Infectious Diseases Outpatient Clinic, which is referral centre for care and treatment of HIV/AIDS in Belo Horizonte, Minas Gerais, Brazil. All patients were more than 18 years old and had no current history of diffuse or focal CNS disease. The control group was evaluated to determine normative values for the neurocognitive tests employed all participants were age older than 18. Subjects 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, Brucki, Campacci & Juliano, 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 this individual control sample.

Neuropsychological assessment.

Subjects were submitted to both functional and neuropsychological assessment (Table 1). All participants completed a comprehensive neurocognitive test battery, covering 7 cognitive domains known to be commonly affected by HIV-associated CNS dysfunction (administration time ~2 hours). The Lawton and Brody scale for Instrumental Activities of Daily Living Scale (IADLs) was used to assess daily life skills (Lawton & Brody, 1969). Full analyses of psychometric values of this neupsychological data was discussed in previous published work (Christo, Géo & Antunes, 2013).

Clinical and Neurological examination

This included medical history, structured neurologic and medical examination, as well as information about demographic, clinical and laboratory characteristics and comorbid conditions such as traumatic brain injury and past CNS opportunistic infections. This evaluation sought to ensure that these conditions, if present, were a static event since its beginning (static and acquired encephalopathy). Determination was performed to assess whether the neurocognitive impairment and functional disability are believed to be due to the effects of HIV on the brain, and are not readily attributable to comorbid conditions. This determination requires not only detailed information about the comorbid conditions themselves, but also clinical judgment about their severity, their likely impact on neurocognition and everyday functioning, and their timing in relation to the course of HIV disease and any functional limitations in everyday life.

Data Analysis

Firstly, to identify the instrument which best accurately distinguished clinical from controls on a same cognitive domain, it was used area under the ROC curve (AUC). Additionally, to develop normative values (z scores) of neuropsychological tests, the control group performance was used. The performance of the clinical group on the tests was classified according to Antinori et al (Antinori et al. 2007). For a diagnosis of HIV associated dementia (HAD), a participant must score 2 SD below standardized scores on 2 of the cognitive domains and have functional impairment on daily life activities. A diagnosis of HIV-associated minor cognitive disorder (MCD) was made when participants did not meet criteria for HAD and met the following criteria: 1) score 1 SD below in at least two of the following cognitive domains and 2) impairment on IADL. For a asymptomatic neurocognitive impairment (ANI) diagnosis, the criteria above must not be following and: 1)

score 1 SD below on at least 2 cognitive domains; 2) no impairment on IADL. HIV normal cognitive functioning occurred when no criteria above were met.

We examined the prevalence of impairment by classifying the individuals in the groups considering test performance and IADL score. Analysis of variance (Anova) was used to investigate statistical differences in demographic and clinical variables among them. T-test, Mann-Whitney and chi-square tests were used to assess whether the two groups (normal versus presence of impairment) were statistically different from each other in demographic and clinical variables. Mann-Whitney U test was an alternative non-parametric test used to investigate differences between groups. A regression logistic model was adjusted for statistical significant variables observed in univariate analysis considering $p<0.25$. The final logistic model was adjusted for significant variables that could differentiates between the normal and impaired HIV cognitive groups considering $p<0.05$.

Results

A total of 110 patients with AIDS (cases) and 64 controls were assessed. Mean age, gender and years of education of participants groups are shown in Table 2. Age distribution was similar comparing cases and controls ($t=0.47$; $p=0.64$); controls have more years of education compared to cases ($t=4.43$; $p<0.01$). Regarding gender, a higher proportion of males were observed among cases (chi-square=20.29; $p<0.01$).

According to standardized neuropsychological scores, the patients were classified into neurocognitive diagnoses (Table 3). ANI was observed in 62/110 cases, HIV dementia in 5/110, MND was observed in 12 and 31 were normal.

Comparisons between impairment and normal groups were presented on Table 4. The former was composed of individuals classified as dementia, minor cognitive disorder and asymptomatic neurocognitive impairment.

When comparing normal and impaired groups, there are differences between them concerning age (t=2.89; p=0.005) and years of education (t=4.30; p<0,001), provenance from cities other than the capital of the state (chi-square=6.39; p=0.01), presence of dyslipidemias (chi-square=4.46; p=0.04), hemoglobin levels (t=2.60; p<0.05). Moreover, there is no differences in gender (chi-square=3.51; p=0.06) time since diagnosis (t=0.20; p=0.84), mean CD4 count (t=0.18; p=0.86), mean viral load (t=1.57; p=0.12).

A regression model was adjusted for statistical significant variables observed on univariate analysis (p<0.25). Initially, the following variables were entered in the model: sex, age, years of study, provenance from cities other than the capital of the state, previous hospitalization, hepatitis B, hemoglobin level and presence of dyslipidemia. The final model indicated that years of study, hemoglobin and dyslipidemia could discriminate between normal and impairment HIV cognitive groups (see Table 5).

Discussion

This study evaluated the presence of cognitive impairment in a sample of HIV-1 seropositive adults seen regularly in an AIDS reference service from the city of Belo Horizonte, Brazil. In this sample we found cognitive impairment in 72% of patients, just over half of the patients analyzed had only evidenced cognitive impairment on neuropsychological tests, but without showing changes in their tasks of daily living. Cognitive disorders who attended with impairment in work and personal life of the patient occurred in about 16% of the sample, and mild cognitive impairment in 11% and the diagnosis of dementia was found in only five patients (5%). These rates were slightly higher than the previously evidenced in other studies in industrialized countries and also in developing countries (Mind Exchange Working Group, 2013). But showed that severe neurocognitive impairment (dementia) is less common. The CHARTER (CNS HIV Antiretroviral Therapy Effects Research) study (Heaton

et al. 2010) showed that the prevalence of HAND remains high despite HAART (52% of the patients in the study had neuropsychological impairment). The prevalence of asymptomatic neurocognitive impairment was highest at 33%, whereas that for HIV-associated dementia was only 2%, and 12% had mild neurocognitive disorder, supporting earlier evidence that whereas severe forms of neurocognitive impairment are occurring less frequently, HAND in its milder forms remains common (Heaton et al, 2010).

In research studies from sub-Saharan Africa, the prevalence of HAD ranges from 2.5%–54% (Kwasa , Cettomai , Lwanya & Lessons, 2012); these estimates vary widely likely due to differences in the sampled populations and methods for assessment of cognitive impairment. Recent study reported HAND in 69% of 200 patients with HIV in a Swiss patient samples who had maintained a good virological response (undetectable HIV RNA in plasma while on cART) over a median of 48 months (Simioni et al. 2012). In Brazilian population other researchs found similar results than shown in this work, with a prevalence of hand in 52% (only screening evaluation) (Rodrigues, Oliveira, Grinsztejn & Silva, 2013) and 58-65% in a full neuropsychological assessment (de Almeida et al. 2013). Similar epidemiological data of HAND where shown in other countries like Uganda 55-80%, United States 57-80% (Saktor et al. 2005), Cameron 85% (Atashili et al. 2013) and China 53% (Wang et al. 2013).

The patient sample was recruited randomly and with few inclusion criteria in an effort to be representative of patients are regularly followed in clinics references in the care of HIV patients in Brazil. Potential confounders such as history of prior opportunistic neurological disease, use or nonuse of HAART and alcohol consumption were not excluded. However these factors did not show statistical differences when we divide the groups of normal and compromised patients. Investigators postulated that a synergy between HIV infection and co-morbid conditions may exist and impact on brain function (Cohen & Gongvatana, 2010;

McArthur & Brew, 2010; McArthur, Steiner, Sacktor & Nath, 2010; Wojna & Nath, 2006). One of the important aspects defined in HAND is the identification of co-morbid etiologies to grade major confounds of HAND into secondary condition (findings are compatible with HAND or incidental), contributing (HAND), and confounding (unable to attribute abnormalities to direct effects of HIV). The main confounding etiologies identified by Antinori et al. (Antinori et al. 2007) were depression, traumatic brain injury (TBI), alcohol and/or substance abuse and co-infection with HCV. This the present study had no association of depression, alcoholism and presence of seizures with HAND and the group of patients also had no cases with TBI or other psychiatric disorders.

In Brazil there are insufficient data on the neurocognitive effects of HIV. These studies are important, since although the social-cultural level is lower than in developed countries, the HIV patient in Brazil has access to antiretroviral treatment free of charge and there are few Brazilian studies of cognitive assessment in patients with AIDS.

Given the rising prevalence of HIV/AIDS in the industrialized and developing world, it is likely that new HIV-associated neurologic syndromes will emerge as time progresses. Neurologic manifestations of AIDS is expected to be a major upcoming health issue among long term HIV seropositive survivors and AIDS patients. Today in developed countries, HAART has changed AIDS from a fatal disease to a more manageable chronic infection (del Palacio, Alvarez & Muñoz-Fernández, 2012). But even with aggressive therapy, the virus cannot be completely eradicated, and body regions that remain relatively isolated from the systemic circulation, such as the CNS, might provide a “sanctuary” for latent or slowly replicating virus.

In general in care services to patients with HIV, the screening for HAND is not performed and therefore it is under diagnosed. The recognition of clinical manifestations

secondary to neurocognitive disorders in HIV patients is currently a major challenge. Not infrequently, psychiatric symptoms are seen as "natural" response to virus infection. The detection of disorders generally requires rigorous investigation, because the symptoms can be subtle or remain unnoticed or unreported (Gallego, Barreiro & López-Ibor 2011). The diagnosis of HAND remains a challenge in HIV outpatient primary care settings in resource-limited regions. Potential reasons for this include: a lack of specialized personnel and diagnostic tests, and the inherent difficulties in making a clinical diagnosis of a complex disorder. We found a significant association of patient low educational level, dyslipidemia, low hemoglobin levels and origin of the interior city with the presence of cognitive impairment that shows the importance of a high specialized and complex treatment of the disease.

Links between components of metabolic syndrome including diabetes and neurocognitive impairment in non-HIV patients has been described as well as the association of dementia in older HIV patients with diabetes mellitus, hypertriglyceridemia and insulin resistance. Central obesity, but not more generalized increases in body mass (BMI), was associated with a higher prevalence of NCI in HIV+ persons (McCutchan et al. 2012). However in the present study did not evaluate the presence of central obesity and only the metabolism of lipid disorders (dyslipidemia) that was associated with the presence of HAND. HIV metabolic syndrome (HIVMetSyn) has recently been identified in HIV-infected individuals and in those with HAND. These abnormalities may occur as a result of chronic HIV infection, long-term use of cART, aging, genetic predisposition or a combination of these factors (Nachega et al. 2009; Tebas, 2008; Valcour et al. 2006). A cardiovascular and cerebrovascular sub-study from the MACS observed a significant association between carotid intima-media thickness and glomerular filtration rate with decreased cognitive performance after adjusting for education, depression and ethnicity (Becker et al. 2009). McArthur et al.

(1993) reported that the strongest predictor of HIV-dementia was low hemoglobin in the pre-cART era and more recent studies suggest that cART reduces the prevalence of anaemia (Belperio & Rhew 2004). There is a paucity of studies in the post-cART era that have examined the association between anaemia and HAND.

With regard to the low educational level similar to other studies in HIV dementia as well as other dementias as Alzheimer's may be due to the brain reserve hypothesis (de Ronchi et al. 1998; Katzman, 1993). Highest level of education may delay the onset of cognitive impairment due to possible promotion of an extra brain reserve. It has also been reported that there is an increased risk of cognitive among older adults who are HIV positive (Becker, Lopez, Dew & Aizenstein, 2004).

Several additional studies have examined the association between HCV and risk of HAND (Cherner et al. 2005; Hilsabeck , Castellon & Hinkin, 2005; Letendre et al. 2005; Tozzi et al. 2005; Aronow, Weston, Pezeshki & Lazarus, 2008; Clifford et al. 2009). In all of these studies, HIV-infected participants who were co-infected with HCV had higher rates of global cognitive impairment. In this study the number of co-infected with hepatitis C virus was small making it impossible to analyze statistic, but the serology for hepatitis B was higher in patients with HAND.

Our study failed to show any statistically meaningful relationship between HAND and both baseline and current CD4 T lymphocyte count and plasma viral load, ART penetration-effectiveness ranking (CPE), depression, age, use of cART and others variables, unlike previous studies. In the pre-cART era, both current and nadir CD4 count were identified as risk factors for HAND (Childs et al. 1999; Heaton et al. 2011). However, in the post-cART era, nadir CD4 rather than current CD4 counts have been shown to be a stronger predictor of HAND (Valcour et al. 2006) but our study did not evaluate the nadir of CD4, only the

baseline and current. In a pre-cART study, McArthur et al. (1997) showed that CSF, but not plasma HIV RNA levels, were significantly higher in those with HAND. However, more recent studies of patients on cART have not found this relationship (Sevigny et al. 2004).

No association was found between alcohol use and HAND. Alcohol has also been suggested as a risk factor for HAND, albeit reports have been conflicting (Jayadev & Garden, 2009).

Some studies have demonstrated beneficial effects on neurocognitive function by ART regimens ranked according to their predicted effectiveness in suppressing HIV replication within the CNS (Letendre et al. 2008; Heaton et al. 2010; Smurzynski et al. 2011). Better neurocognitive performance has been observed over a 15-week period in adult individuals beginning ART with regimens of higher CPE (Letendre et al. 2008). A cross-sectional study of 2636 adults (AIDS Clinical Trials Group Longitudinal Linked Randomized Trials [ALLRT cohort]) on effective ART (<50 HIV RNA copies/ml) demonstrated better neurocognitive performance in those receiving higher CPE ART (Smurzynski et al. 2011).

Risk factors for HAND found in this sample of patients, especially those not found, may be by specific characteristics of the study population or a limited sample. Future studies are needed to better characterize these risk factors, aiming to detect more clearly if there is a different pattern of these factors in the Brazilian population in comparison to international studies.

This study had a broad neuropsychological assessment, with a variable selection with the best discriminative power for each domain, a rigorous definition of the diagnostic criteria of cognitive disorders and a random sampling of the population, increasing the power of generalizing the results. However, size limitations of the sample group, especially in the

control group appeared, as well as lower education level of the control group compared to the clinical group.

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, 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.

Table 1: Neuropsychological battery

Cognitive domain	Neuropsychological Test	Selected Neuropsychological Test
Processing speed	Coding WAIS-III Trail Making test part A Stroop test 1 and 2	Coding WAIS-III
Working Memory/Attention	Paced Auditory Serial Addition Test- part A Dígit Span WAIS-III Five Points Test	Paced Auditory Serial Addition Test- part A
Executive function	Trail Making test part B Stroop test part 3	Five Points Test-
Episodic Memory and Learning	Rey Complex Figure record after 3 minutes Rey Auditory Verbal Learning Test	Rey Complex Figure record after 3 minutes
Language	Semantic Verbal Fluency Foods Semantic Verbal Fluency Animals Fonemic Verbal Fluency F.A.S.	Semantic Verbal Fluency Foods
Fine motor coordination	Nine Hole Peg Test	Nine Hole Peg Test
Visuo-construtive skill	Rey Complex Figure Copy	Rey Complex Figure Copy

Table 2: **Descriptive statistics of demographic variables**

Groups	N	Mean age (sd)	Years education (sd)	% men
Cases	110	43.03 (9.07)	6.61 (3.51)	67.3
Controls	64	42.05 (15.20)	8.98 (3.23)	32.8

Table 3: **Prevalence of HIV-associated neurocognitive disorders**

Neurocognitive diagnoses	Frequency	Percent
Dementia-HIV	5 (4,5)	4,5
MND*	12 (10,9)	10,9
Asymptomatic (ANI)	62 (56,4)	56,4
Normal	31 (28,2)	28,2

* MND = mild neurocognitive disorder

Table 4: **Clinical and laboratory characteristics of the sample**

Variables	Presence of impairment (n=79) Mean(SD) or Count(Percentage)	Normal (n=31) Mean(SD) or Count(Percentage)	*t* or χ^2	p (two-tailed)
Sex Male	49 (62.03)	25 (80.64)	-3.51	0.06
Ethnic group				
Withe	36 (45.60)	20 (64.50)	4.26	0.12
Black	20 (25.30)	3 (9.70)		
Brown	23 (29.10)	8 (25.80)		
Age (years)	44.38 (9.43)	39.58 (7.08)	2.89	0.005*
Education (years)	5.77 (3.22)	8.74 (3.36)	4.30	0.000*
Provenance				
Capital of state	42 (54.50)	25 (80.6)	6.39	0.01*
Others	35 (45.50)	6 (19.4)		
Family Income			0.55	0.58
Until 2 minimum wage	26 (32.90)	10 (32.30)		
2 to 5 minimum wages	50 (63.30)	18 (8.10)	1.51	0.47
5 to 10 minimum wages	3 (3.80)	3 (9.70)		
Time of the diagnostic HIV (months)	70.71 (46.11)	72.68 (45.94)	0.20	0.84
Heterosexual exposure category	30 (38.0)	13 (41.9)	0.15	0.70

Previous hospitalization	52 (65.8)	31 (51.6)	1.95	0.18
Depression	8 (10.10)	5 (16.10)	0.77	0.38
Smoking	22 (27.80)	8 (25.80)	0.047	0.83
Alcoholism	16 (20.30)	3 (9.70)	1.74	0.19
Dyslipidemia	19 (24.10)	2 (6.50)	4.46	0.04*
Past ONI [d]	16 (20.3)	4 (12.9)	0.81	0.84
Peripheral Neuropathy	29 (36.71)	7 (22.58)	2.02	0.16
Use ofARV	59 (93.70)	26 (100)	1.78	0.19
ARV[a] Score	4.97 (3.22)	6 (2.70)	1.13	0.19
Serology of hepatiise B	14 (20.60)	8 (29.60)	2.86	0.09
Hepatitis C	0	1 (4.20)	0.88	0.34
Initial CD4 count (cells/m^3)	291.67 (294.99)	359.71 (263.36)	1.11	0.27
Current CD4 count (cells/m^3)	491.96 (235.88)	501.11 (228.74)	0.18	0.86
Initial Viral Load (log)	3.98 (1.24)	3.96 (1.35)	0.08	0.94
Actual Viral Load (log)	2.62 (1.17)	2.62 (1.30)	0.01	0.99
Hemoglobin	13.61 (2.08)	14.77 (1.65)	2.60	0.01*
Albumin[a]	419.62 (493.87)	292.86 (459.12)	1.18	0.24
Seizures	14 (17.7)	3 (9.7)	1.10	0.25
Arterial hypertension	8 (10.1)	2 (6.5)	0.36	0.55
Diabetes Mellitus	1 (1.30)	0	0.40	0.53

Legend: [a)] We used U Mann-Whitney to compare groups' performance; [c)] Variation was observed on participants' number of each group; * *p<0.001; *p<0.01. [d] opportunistic neurological infections

Table 5: **Multiple regression analysis**

Variáveis	B	S.E.	Wald	Df	Sig.	Exp(B)
Education (years)	0.27	0.09	10.15	1	0.00	1.31
Hemoglobin	0.36	0.16	5.52	1	0.02	1.46
Dysplidemia	-2.24	0.90	6.16	1	0.01	0.11
Constant	-7.95	2.40	11.00	1	0.00	0.00

References:

1. Antinori A, Arendt G, Becker JT, et al. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 69:1789-1799.
2. Aronow HA, Weston AJ, Pezeshki, BB, Lazarus TS. (2008). Effects of coinfection with HIV and hepatitis C virus on the nervous system. *AIDS Read*.18:43-48.
3. Atashili J1, Gaynes BN, Pence BW, Tayong G, Kats D, O'donnell JK, Ndumbe PM, Njamnshi AK. (2013). Prevalence, characteristics and correlates of a positive-dementia screen in patients on antiretroviral therapy in Bamenda, Cameroon: a cross-sectional study. *BMC Neurol.* 15;13:86.
4. Becker JT, Kingsley L, Mullen J, et al. (2009). Vascular risk factors, and cognitive dysfunction in gay and bisexual men. *Neurology*. 73:1292-1299.
5. Becker JT, Lopez OL, Dew MA, Aizenstein HJ. (2004). Prevalence of cognitive disorders differs as a function of age in HIV virus infection. *AIDS*. 1;18 Suppl 1:S11-8.

6. Belperio PS, Rhew DC. (2004). Prevalence and outcomes of anemia in individuals with human immunodeficiency virus: a systematic review of the literature. *Am J Med.* 116 Suppl 7A:27S-43S.
7. Bertolucci PHF, Brucki SMD, Campacci SR, Juliano Y. (1994). O Mini-exame do Estado Mental em uma população geral. Impacto da escolaridade. *Arq. Neuropsiquiatr*. 52:1-7.
8. Boletim epidemiológico AIDS-DST Ano VIII No1 publicado 28/11/2011. http://www.aids.gov.br/publicacao/2011/boletim_epidemiologico_2011.
9. Brew BJ, Crowe SM, Landay A, et al. (2009) Neurodegeneration and ageing in the HAART era. *Journal of Neuroimmune Pharmacology*. 4: 163–174
10. Cherner M, Letendre S, Heaton RK, et al. (2005). Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. *Neurology*.64:1343-1347
11. Childs EA, Lyles RH, Selnes OA, et al. (1999). Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. *Neurology*. 52(3):607-613.
12. Christo PP. (2010). Cognitive alterations associated with HIV-1 infection and AIDS. Rev *Assoc Med Bras*. 56(2):242-7.
13. Christo PP, Géo LAL, Antunes CMF. (2013). Neurocognitive performance in patients with AIDS in Brazil: a case-control study. *Clinical Neuropsychiatry*. 10, 2, 107-110.
14. Clifford DB, Smurzynski M, Park LS, et al. (2009). Effects of active HCV replication on neurologic status in HIV RNA virally suppressed patients. *Neurology*. 73:309-314
15. Cohen RA, Gongvatana A. (2010). The persistence of HIV-associated neurocognitive dysfunction and the effects of comorbidities. *Neurology*.;75(23):2052-3

16. de Almeida SM, Ribeiro CE, de Pereira AP, Badiee J, Cherner M, Smith D, Maich I, Raboni SM, Rotta I, Barbosa FJ, Heaton RK, Umlauf A, Ellis RJ. (2013). Neurocognitive impairment in HIV-1 clade C- versus B-infected individuals in Southern Brazil. *J Neurovirol*.19(6):550-6.
17. De Ronchi D, Fratiglioni L, Rucci P, Paternicò A, Graziani S, Dalmonte E. (1998). The effect of education on dementia occurrence in an Italian population with middle to high socioeconomic status. *Neurology*. 1998;50(5):1231-8.
18. del Palacio M, Alvarez S, Muñoz-Fernández MÁ. (2012). HIV-1 infection and neurocognitive impairment in the current era. *Rev Med Virol*. 22(1):33-45.
19. Gallego L, Barreiro P, López-Ibor JJ. (2011). Diagnosis and clinical features of major neuropsychiatric disorders in HIV infection. *AIDS Rev*. 13(3):171-9.
20. Global report: UNAIDS report on the global AIDS epidemic 2013.
21. Grant I, Sacktor N, McArthur JC. (2005). HIV neurocognitive disorders. In: Gendelman HE, Grant I, Everall I, Lipton SA, Swindells S, editors. The neurology of AIDS. 2nd ed., Oxford: Oxford University Press. 359-373.
22. Heaton RK, Clifford DB, Franklin DR Jr, et al. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. *Neurology*. 75:2087-2096.
23. Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I; CHARTER Group. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER. *Study.Neurology*. 7;75(23):2087-96.

24. Heaton RK, Franklin DR, Ellis RJ, et al. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol* 17:3-16.
25. Hilsabeck RC, Castellon SA, Hinkin CH. (2005). Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clin Infect Dis*. 41 Suppl 1:S38-S44.
26. Jayadev S, Garden GA. (2009). Host and viral factors influencing the pathogenesis of HIV-associated neurocognitive disorders. *J Neuroimmune Pharmacol*. 4(2):175-189
27. Katzman R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology*. 43(1):13-20.
28. Kwasa J, Cettomai D, Lwanya E. (2012). Lessons learned developing a diagnostic tool for HIV-associated dementia feasible to implement in resource-limited settings: pilot testing in Kenya. *PLoS One.* 7(3):e32898.
29. Lawton, M.P., and Brody, E.M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* 9:179-186.
30. Letendre S, Marquie-Beck J, Capparelli E, et al. (2008). Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 65:65-70.
31. Letendre SL, Cherner M, Ellis RJ, et al. (2005). The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance: biological correlates of disease. *AIDS*.19 Suppl 3:S72-S78.
32. McArthur JC, Brew BJ. (2010). HIV-associated neurocognitive disorders: is there a hidden epidemic? *AIDS*. 24(9):1367-1370.
33. McArthur JC, Hoover DR, Bacellar H, et al. (1993). Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. *Neurology*. 43(11):2245-2252

34. McArthur JC, McClernon DR, Cronin MF, et al. (1997). Relationship between human immunodeficiency virus-associated dementia and viral load in cerebrospinal fluid and brain. *Ann Neurol*. 42(5):689-698.
35. McArthur JC, Sacktor N, Selnes O. (1999). Human immunodeficiency virus-associated dementia. *Semin Neurol*. 19(2):129-50.
36. McArthur JC, Steiner J, Sacktor N, Nath A. (2010). HIV-associated neurocognitive disorders. Mind the gap. Ann Neurol. 67:699-714.
37. McArthur JC. (2004). HIV dementia: an evolving disease. *J Neuroimmunol*. 157:3-10.
38. McCutchan JA, Marquie-Beck JA, Fitzsimons CA, Letendre SL, Ellis RJ, Heaton RK, Wolfson T, Rosario D, Alexander TJ, Marra C, Ances BM, Grant I; CHARTER Group. (2012). Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. *Neurology*.78(7):485-92.
39. Mind Exchange Working Group. (2013). Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. *Clin Infect Dis.* 56(7):1004-17.
40. Nachega JB, Trotta MP, Nelson M, et al. (2009). Impact of metabolic complications on antiretroviral treatment adherence: clinical and public health implications. *Curr HIV/AIDS Rep.* 6:121-129.
41. Rodrigues RA, Oliveira RL, Grinsztejn B, Silva MT. (2013) Validity of the International HIV dementia scale in Brazil. *Arq Neuropsiquiatr*. 2013;71(6):376-9.
42. Sacktor N, McDermott MP, Marder K, et al. (2002). HIV-associated cognitive impairment before and after the advent of combination therapy. *J Neurovirol*. 8:136-142.

43. Sacktor NC, Wong M, Nakasujja N, Skolasky RL, Selnes OA, Musisi S, Robertson K, McArthur JC, Ronald A, Katabira E. (2005). HIV Dementia Scale: a new rapid screening test for HIV dementia. *AIDS.* 2;19(13):1367-74.
44. Selnes OA. (2005). Memory loss in persons with HIV/AIDS: assessment and strategies for coping. *AIDS Read*. 15(6):289-92, 294.
45. Sevigny JJ, Albert SM, McDermott MP, et al. (2004). Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia. *Neurology*. 63:2084-2090.
46. Simioni S, Cavassini M, Annoni JM, et al. (2010) Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*;24:1243-1250.
47. Smurzynski M, Wu K, Letendre S, et al. (2011). Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. *AIDS*. 25(3):357-365.
48. Tebas P. (2008). Insulin resistance and diabetes mellitus associated with antiretroviral use in HIV-infected patients: pathogenesis, prevention, and treatment options. *J Acquir Immune Defic Syndr*. 49 Suppl 2:S86-S92 .
49. Tozzi V, Balestra P, Lorenzini P, et al. (2005). Prevalence and risk factors for human immunodeficiency virus-associated neurocognitive impairment, 1996 to 2002: results from an urban observational cohort. *J Neurovirol*. 11(3):265-273 .
50. Valcour V, Yee P, Williams AE, et al. (2006). Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection – The Hawaii Aging with HIV Cohort. J *Neurovirol* 12(5):387-391.

51. Valcour VG, Sacktor NC, Paul RH, et al. (2006). Insulin resistance is associated with cognition among HIV-1-infected patients: the Hawaii Aging With HIV cohort. *J Acquir Immune Defic Syndr*. 43(4):405-410.

52. Wang Z, Zheng Y, Liu L, Shen Y, Zhang R, Wang J, Lu H. (2013). High prevalence of HIV-associated neurocognitive disorder in HIV-infected patients with a baseline CD4 count ≤ 350 cells/μL in Shanghai, China. *Biosci Trends.* 7(6):284-9.

53. Wojna V, Nath A. (2006). Challenges to the diagnosis and management of HIV dementia. *AIDS Read*. 16:615-6, 621-4, 626, 629-632.

4- COMPARISON OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS AND ALZHEIMER DISEASE IN A VERBAL LEARNING EPISODIC TEST: SUBCORTICAL X CORTICAL PROFILE

Abstract:

Background: HIV-associated Neurocognitive Disorders (HAND) is a typical neurological complication in HIV patients that damage subcortical structures of the brain. However Alzheimer Disease (AD) led to a cortical dementia with a central deficit in episodic memories.

Methods: We compared HAND (n=79) and AD (n=78) patients in Rey Auditory Verbal Learning Test (RAVLT) to find a differentiation of subcortical x cortical profiles, based in the differentiate in storage and retrieval of the information.

Results: The groups differ in A1 (*U*=2217,50, p=0,002), TOT (*U*=2483,00, p=0,036), LOT (*U*=2286,00, p=0,005) and REC (*U*=567,50, p<0,001), with better results for the HAND group. The other variables did not differ in our study (p>0,05). Excluding the dementia cases, we found the same result, better performance in HAND group in the same variables, A1 (*U*=1963,50, p=0,003), TOT (*U*= 2159,00, p=0,026), LOT (*U*=1947,50, p=0,002) and REC (*U*=510,50, p<0,001). In a comparison only using dementia subjects, even with a very small numbers of (n=9) we found a significant difference in REC result (*U*=2,00, p=0,05) with a better performance in HAND group. In effect size analyses of full sample we found small effects for A1 (r= 0,24), TOT (r=0,17) and LOT (r=0,22) and large effects for REC (r=0,70).

Conclusion: The results corroborated the hypothesis, showing the same performance in episodic memories components (p<0,05) but a benefit of HAND group in the presence of a clue to recognize the stimuli (p>0,05), pointing to a subcortical fronto-striatal damage.

Introduction

The HIV-Associated Dementia (HAD) is a well known neurological complication caused by the directed and undirected action of the virus in CNS and its inflammatory responses (Xia, 2011). Other earlier stages of the disease exist in a large number of individuals with several impacts in their daily living activities with a presence of mild impairment including since the asymptomatic neurocognitive impairment (ANI) to HIV-associated mild neurocognitive disorder (MND), forming a cluster named HIV-associated Neurocognitive Disorders (HAND) (Maj et al. 1994). In Brazilian population, HAND was detected in 98 of 187 patients (52%) using a validated screening instrument (Rodrigues et al. 2013), the International HIV Dementia Scale (IHDS) while in a sample submitted to a full neuropsychological evaluation the percentage of detection was 58-65% (de Almeida et al. 2013). In a previous study from our group (Christo et al., 2013) we detected the presence of HAND in 71,8% of HIV infected population (n=110) using a broad neuropsychological and clinical evaluation including tasks from Antinori criteria (Antinori et al. 2007).

The incidence of HAD has decreased after the use of HAART with a larger expectancy of life but the prevalence of HAND has actually increased due to the enhanced survival of HIV-1 infected patients receiving HAART (Saktor et al. 2002), probably associated to more time of life exposed by the neuroinfection (Brew et al 2008). From aging of HIV population emerges a new risk factor for other types of dementia, especially Alzheimer's Disease (AD), tightly associated to aging processes and starts new challenges for professionals of health (Xu & Ikezu, 2009). Therefore, is important to assess differences between HAD and another types of dementia. This knowledge will be useful both considering the elucidation of the brain mechanisms of HAD and for clinical purposes.

The dementia in HIV presents a “subcortical” pattern of symptomatology with a primary damage on white matter and fronto-striatal structures despite some findings have

demonstrated reduced volume both in subcortical and cortical areas in brain (Cohen et al. 2010). Deficits in episodic memory is a common symptom of HAND affecting treatment adherence, especially in prospective memory, or, “remember to remember” (Woods et al. 2008). Sadek et al (Sadek et al. 2004) have found in HAND, Huntington Disease, other subcortical dementia process and Alzheimer Disease deficits on remote memory but with a benefit of a “clue” to retrieval the information on HAND and Huntington Disease, pointing to a dissociation between cortical and subcortical dementias, involving the retrieval process in fronto-subcortial structures and medial temporal structures involved in learning of the information. A subcortical profile in verbal learning memory process are described in HAND as well as a typical difficulty in the retrieval of the information (Delis, 1995).

This study intend to assess differences between a sample of subjects with pathological aging presenting a cortical pattern of disease (including both amnestic mild cognitive impairment and Alzheimer disease) and a group of patients presenting HAND or HAD. Our hypothesis in this work is to seek a sub-cortical pattern in verbal learning episodic memory in HAND, characterized by difficult to evoke episodic memories but with a benefit of a “clue” for a retrieval process, a typically deficit on subcortical fronto-striatal structures. A true deficit in storage of the information is associated to cortical-temporal structures, not benefited by clues, a typical deficit in AD.

Method

Participants

Two groups were selected to this study at two different Hospitals in Belo Horizonte, Minas Gerais, Brazil. The first group are composed by seventy-nine (n=79) regular patients of Eduardo de Menezes (Infectious Diseases Outpatient Clinic), a referral centre of treatment of HIV/AIDS. These patients have participated in other study (Christo et al. 2013) with a

rigorous control for a epidemiological estimation of HAND. All participants are older than 18 years and have no current history of diffuse or focal CNS disease and/or systemic disease. All these selected patients have diagnostic of HAND based on Antinori criteria (Antinori et al 2007) after a comprehensive neuropsychological assessment. The stages of HAND in this population were 1 - HIV associated dementia (n=5), 2- HIV-associated mild cognitive disorder (n=12), 3- asymptomatic neurocognitive impairment (n=62).

A second clinical group involved older adults diagnosed with amnestic mild cognitive impairment (MCI) or dementia probable due to AD. These participants underwent detailed clinical and neuropsychological assessment as described elsewhere (de Paula et al., 2013). Briefly it involve the assessment of clinical history according to the Mckhann and colleagues (2011) and Albert and colleagues (2011) guidelines and cognitive assessment by the use of the the Mini-Mental State Examination (Folstein, Folstein & McHugh, 1976), the Mattis Dementia Rating Scale (Mattis, 1986), subtests from the CERAD Neuropsychological Battery (Morris, 1989) and the Clinical Dementia Rating (Morris, 1993). Only patients with Clinical Dementia Rating of 1 (AD) or 0,5 (MCI) were invited for participation.

Episodic Memory Assessment

We used the Brazilian version of the Rey's Auditory Verbal Learning Test (RAVLT) in both groups to access different aspects of verbal episodic memory among the two groups. The test was developed for Brazilian-Portuguese speakers taking account the words length and frequency (Malloy-Diniz et al., 2007) and it was validated for young and older adults of this population (Salgado et al., 2011; de Paula et al., 2012). It consists of a 15 substantives lists read aloud five times for the patient (A1, A2, A3, A4, A5); a distractor trial of 15 new words (B1), a short (A6) and long term recall (A7) and recognition memory (REC). We compared several measures of the test in order to document different process of episodic

memory: *short-term memory* (trials A1 and B1), *learning processes* (Sum of words between A1 and A5; the LOT index [Total-5*A1]), *free recall* (A6, A7), and *recognition memory* (REC).

Data analysis

In previous analyses using Mann-Whitney U test and Chi Square analyses we found a significant difference of age, sex and formal education in both groups (Table 1). That difference was expected by the profile of the distinct populations, diseases and Health Centers. To compare these two different populations, we calculated Z-Scores based on the Brazilian normative studies for both young and older adults stratified by age and education (Magalhães & Hamdan, 2010). The comparison of the groups was made with Student t test considering $p<0.05$ and the effect size was calculate with *r* coefficient. We used the Statistical Package for Social Sciences (SPSS) software version 20.0.

Results

The descriptive data are shown in Table 1. A total of 157 subjects were selected, 79 in HAND group and 78 in AD group. No significant difference in the frequency of dementia stage between groups (X^2 = 37,56, p= 0,853) were observed. Age (*U*=39,50, p<0,001), years of study (*U*=1932,00, p<0,001) and sex (X^2=15,59; p<0,001) was significantly different between groups with an expected profile of younger (m= 42,38 years; sd= 9), more schooled (m= 6,52 years of school; sd= 3,39) and typically male (73,4%) in HAND group. The AD group are majority female (57,7%), elderly (m= 73,54 years; sd= 8,68) and less schooled (m= 4,54 years; sd=3,91).

Then we transform the scores in Z scores using a normative data of a Brazilian population in RAVLT (Magalhães & Hamdan, 2010) corrected by age and scholarity in order to correct the differences between the groups. The results are shown in Table 2. The groups differ in A1 (*U*=2217,50, p=0,002), TOT (*U*=2483,00, p=0,036), LOT (*U*=2286,00, p=0,005) and REC (*U*=567,50, p<0,001), with better results for the HAND group. The other variables did not differ in our study (p>0,05). Excluding the dementia cases, we found the same result, better performance in HAND group in the same variables, A1 (*U*=1963,50, p=0,003), TOT (*U*= 2159,00, p=0,026), LOT (*U*=1947,50, p=0,002) and REC (*U*=510,50, p<0,001). In a comparison only using dementia subjects, even with a very small numbers of (n=9) we found a significant difference in REC result (*U*=2,00, p=0,05) with a better performance in HAND group.

In effect size analyses of full sample we found small effects for A1 (r= 0,24), TOT (r=0,17) and LOT (r=0,22) and large effects for REC (r=0,70).

Discussion

We have hypothesized that HAND group shown a subcortical pattern of performance in episodic verbal memory and learning, in other words, difficult to evoque long term learned facts but with a considerable help with clues to remember (Sadek et al. 2004). This pattern is expected because of the damage in whiter matter and fronto-striatal structures in the HIV neuroinfection (Xia et al. 2011). However in cortical dementia as classically described in Alzheimer Disease the pattern is a difficulty to evoque facts since the information is not truly

learned; the deficit is in the storage of the information not on the retrieval and the presence of clues is irrelevant. The neuronal structures involved in storage of information was related to hippocampus cortex and temporal lobe (Mulder et al. 2014), the former typical target in Alzheimer Disease.

Our data analyses corroborate this hypothesis. In short term components and learning stages, the performance in HAND group was slightly better than other group. The evocation of the information which is a measure of long term memory had a similar result in both groups. However in the presence of a clue to recognize the learned words, HAND group demonstrated a superior performance suggesting that the information was stocked and the difficulty was in the retrieval suggesting a specific damage on fronto-striatal structures. A retrieval deficit was descripted even in visuospatial memory in HIV patients, pointing to a fronto-striato-thalamo-cortical pathway damaged (Woods et al. 2013).

The effect size analyses shown that the impact of group differences are small for short term memory and learning components, probably related to a more specific damage on temporal structures in AD group. However the effect size in recognition component was large, pointing to a very different pattern between groups what corroborate with the initial hypothesis. This results was very similar to others works (Sadek et al. 2004; Delis et al. 1995), corroborating a subcortical profile.

Limitations of this study are clear and future works must improve the methodology. We compare two very different populations, especially in a developing country like Brazil. Age, sex and schooling can impact in the neuropsychological performance and the statistical correction made is limited. Additional work must focus on longitudinal evaluation of HAND and the presence of possible AD or use same or close age of groups.

Clinical and treatment implications of these results needs to be better discussed. The aging of the HIV infected population implies in the risk factor for AD (Xu & Ikezu, 2009)

and the possibility of HAND and AD was alarmant as the neurocognitive deficits involved are different just like their causes. HAND population was likely to depend more of social services compared to other HIV infected individuals (Umaki et al. 2013). Particularities in HAND profile of episodic memory can change dramatically the treatment of patients especially in adherence of medication (Woods et al. 2008) directly associated to memory lapse. Others impacts in activities of daily living are probably associated too.

Our study focused in episodic verbal memory. Future studies should address other differences in cognition assessing subcortical x cortical profile comparisons between HAND and another types of pathological aging processes. .

Table 1 - **Descriptive statistics of demographic variables in AD and HAND groups**

	AD	HAND	
	Mean or n	Mean or n	p
	78	79	
Age	73,54 (8,68 sd)	44,38(9,01 sd)	,000
Years of study	4,54 (3,91 sd)	5,77 (3,39 sd)	,000
ACD	64	62	0,853
MCD	10	12	-
Dementia	4	5	-
Male	33	62	0,000
Female	45	21	-

*ACD = asymptomatic cognitive impairment/disorder; MCD = mild cognitive impairment/disorder

Table 2 - **Comparison of Z scores between groups and effect size**

	AD	sd	HAND	sd	p	Effect Size
A1	-1,108	1,072	-,676	,777	,002*	0,242
TOT	-1,396	1,055	-1,111	1,027	,036*	0,168
A6	-1,428	,878	-1,362	1,291	,423	0,064
A7	-1,218	1,497	-1,354	1,122	,859	0,014
LOT	-,511	1,029	-,043	1,111	,005*	0,223
REC	-4,703	2,798	-,550	1,591	,000*	0,705

*p<0,05

References:

1. Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 7(3):270-9.
2. Antinori A, Arendt G, Becker JT, et al. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology.* 69:1789-1799
3. Brew BJ, Crowe SM, Landay A, et al. (2009). Neurodegeneration and ageing in the HAART era. *Journal of Neuroimmune Pharmacology*. 4: 163–174

4. Christo PP, Géo LAL, Antunes CMF. (2013). Neurocognitive performance in patients with AIDS in Brazil: a case-control study. *Clinical Neuropsychiatry*. 10, 2, 107-110.
5. Cohen RA, Harezlak J, Gongvatana A, Buchthal S, Schifitto G, Clark U, Paul R, Taylor M, Thompson P, Tate D, Alger J, Brown M, Zhong J, Campbell T, Singer E, Daar E, McMahon D, Tso Y, Yiannoutsos CT, Navia B; HIV Neuroimaging Consortium. (2010). Cerebral metabolite abnormalities in human immunodeficiency virus are associated with cortical and subcortical volumes. *J Neurovirol.*16(6):435-44.
6. de Almeida SM, Ribeiro CE, de Pereira AP, Badiee J, Cherner M, Smith D, Maich I, Raboni SM, Rotta I, Barbosa FJ, Heaton RK, Umlauf A, Ellis RJ. Neurocognitive impairment in HIV-1 clade C- versus B-infected individuals in Southern Brazil. (2013). *J Neurovirol*. Dec;19(6):550-6.
7. de Paula, J.J., Miranda, D.M., Nicolato, R., Moraes, E.N., Bicalho, M.A., Malloy-Diniz, L.F. (2013a). Verbal learning on depressive pseudodementia: accentuate impairment of free recall, moderate on learning processes, and spared short-term and recognition memory. *Arq Neuropsiquiatr*. 71(9A):596-9.
8. Delis, D. C., Peavy, G., Heaton, R., Butters, N., Salmon, D. P., Taylor, M., et al. (1995). Do patients with HIV-associated minor cognitive/motor disorder exhibit a "subcortical" memory profile? Evidence using the California Verbal Learning Test. *Assessment*. 2, 151–165.
9. Magalhães SS, Hamdan AC. (2010). The Rey Auditory Verbal Learning Test: normative data for the Brazilian population and analysis of the influence of demographic variables. *Psychology & Neuroscience*. 3, 1, 85 - 91
10. Maj M, Satz P, Janssen R, Zaudig M, Starace F, et al. (1994). WHO Neuropsychiatric AIDS study, cross-sectional phase II. Neuropsychological and neurological findings. *Arch Gen Psychiatry*. 51:51–61.

11. McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R. Jr., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7(3):263-9.
12. Mulder ER, de Jong RA, Knol DL, van Schijndel RA, Cover KS, Visser PJ, Barkhof F, Vrenken H; for the Alzheimer's Disease Neuroimaging Initiative. (2014). Hippocampal volume change measurement: Quantitative assessment of the reproducibility of expert manual outlining and the automated methods FreeSurfer and FIRST. *Neuroimage*. 9. pii: S1053-8119.
13. Rodrigues RA, Oliveira RL, Grinsztejn B, Silva MT. (2013). Validity of the International HIV dementia scale in Brazil. *Arq Neuropsiquiatr*.71(6):376-9.
14. Sacktor N, McDermott MP, Marder K, et al. (2002). HIV-associated cognitive impairment before and after the advent of combination therapy. *J Neurovirol*. 8:136-142.
15. Sadek JR, Johnson SA, White DA, Salmon DP, Taylor KI, Delapena JH, Paulsen JS, Heaton RK, Grant I. (2004). Retrograde amnesia in dementia: comparison of HIV-associated dementia, Alzheimer's disease, and Huntington's disease. *Neuropsychology*.18(4):692-9.
16. Umaki TM, Gangcuangco LM, Chow DC, Nakamoto BK, Marotz L, Kallianpur KJ, Shikuma CM. (2013). Poorer Neuropsychological Performance Increases Risk for Social Services Among HIV-infected Individuals. *Hawaii J Med Public Health*.2(12):422-6

17. Woods SP, Moran LM, Carey CL, Dawson MS, Iudicello JE, Gibson S, Grant I, Atkinson JH, HIV Neurobehavioral Research Center Group. (2008). Prospective memory in HIV infection: Is "remembering to remember" a unique predictor of self-reported medication management? *Arch Clin Neuropsychol*.23(3):257-70.
18. Woods SP, Hoebel C, Pirogovsky E, Rooney A, Cameron MV, Grant I, Gilbert PE; HIV Neurobehavioral Research Program Group. (2013). Visuospatial temporal order memory deficits in older adults with HIV infection. *Cogn Behav Neurol*. 26(4):171-80.
19. Xia C, Luo D, Yu X, Jiang S, Liu S. (2011). HIV-associated dementia in the era of highly active antiretroviral therapy (HAART). *Microbes Infect*.13(5):419-25.
20. Xu, J., Ikezu T. (2009). The comorbidity of HIV-associated neurocognitive disorders and Alzheimer's disease: a foreseeable medical challenge in post-HAART era. *J Neuroimmune Pharmacol.* 4(2): 200–212.

5 - CONCLUSÕES E REPERCURSSÕES

Verificamos que em população brasileira, no estado de Minas Gerais, a frequência total de HAND foi de 71,8%, sendo 4,5% casos de demência, 10,9% comprometimento cognitivo leve e 56,4% casos de comprometimento cognitivo assintomático. Esta freqüência diagnóstica encontrada foi superior ao já reportado na literatura brasileira, de 52 a 65% (Rodrigues, Oliveira, Grinsztejn & Silva, 2013, de Almeida et al. 2013), o que pode ser explicado por uma metodologia mais completa de avaliação utilizada no presente estudo, bem como a amostra ser hospitalar, provavelmente com mais comprometidos. A necessidade de estudos específicos na população brasileira é requer atenção já que o Brasil possui uma realidade muito diferente dos países de primeiro mundo, ou países de extrema pobreza africanos, onde geralmente os estudos epidemiológicos internacionais ocorrem (Alkali, Bwala, Nyandaiti & Danesi, 2013; Joseph et al. 2013). Este resultado deve ser levado em consideração para a fundamentação de políticas públicas futuras já que a maioria da população infectada apresenta danos cognitivos que são diretamente ligados à danos em atividades laborativas, atividades de vida diária, inserção social, qualidade de vida e principalmente, aderência ao tratamento medicamentoso (Woods et al. 2008). Desconhecemos qualquer medida de política pública até esta presente data, com enfoque de divulgação e tratamento de danos cognitivos associados ao HIV no Brasil. Dos estimados 630.000 habitantes infectados por HIV no Brasil (UNAIDS/WHO 2011), aproximadamente 450 mil teriam HAND de acordo com a prevalência estimada neste estudo, um enorme contingente populacional que dificilmente receberá tratamento apropriado.

Os fatores de risco associados à HAND nesta população foram, de maneira mais impactante, à presença de dislipidemia, nível de hemoglobina e nível educacional. Também foram encontrados fatores associados como idade e se o paciente é morador na capital do Estado ou interior, com menor impacto. Sabendo que o nível educacional é um conhecido

protetor cognitivo (de Ronchi et al. 1993) e que o nível educacional brasileiro é baixo, bem como serviços de saúde básica deficitários, o padrão populacional brasileiro encontra um risco considerável à HAND, especialmente em pacientes que não moram nas capitais estaduais. Outros dados chamaram atenção, em especial o fato de não encontrarmos associação do uso da medicação, bem como seu poder de penetrância, como fator de risco/proteção, o que já é discutido na literatura onde o uso do antiretroviral não tem uma associação claramente positiva com a prevenção e tratamento da HAND (Smurzynski et al. 2011).

No segundo trabalho, verificamos o padrão de comprometimento cognitivo relacionado à lesões subcorticais da HAND, como já descrito na literatura (Cohen et al, 2010). Embora o comprometimento cognitivo surja em diversos domínios (Christo, Géo & Antunes, 2013), o padrão de desempenho é mais comprometido em funções executivas e velocidade de processamento, relacionadas à circuitaria fronto-estriatal. Como metodologia de análise, focamos na aprendizagem e memória episódica auditivo-verbal, componente comprometido em demências corticais, com DA, mas também comprometida na HAND. Em comparativo a grupos de déficits cognitivos provavelmente relacionados à DA, o padrão de comprometimento da HAND ocorreu conforme as hipóteses iniciais com melhor desempenho durante a aprendizagem, mas com igual dificuldade durante a evocação espontânea das memórias episódicas. Entretanto houve grande benefício do reconhecimento do estímulo, indicando que a memória foi armazenada e, tendo um facilitador do resgate da informação, ela foi recuperada. Quando o dano cognitivo ocorre em estruturas corticais, especialmente temporais como o hipocampo, o armazenamento da informação é comprometido. Já em lesões subcorticais fronto-estriatais o armazenamento ocorre, mas o resgate da informação é comprometido (Sadek et al, 2004, Delis et al. 1995).

Esta diferenciação em uma tarefa de aprendizagem verbal pode ser instrumento complementar em diagnóstico diferencial entre HAND e DA, uma crescente complicação diagnóstica devida ao envelhecimento da população infectada pelo HIV. Entretanto, diversos outros domínios cognitivos precisam de maior esclarecimento e outras possibilidades de técnicas neuropsicológicas diferenciais são necessárias e possíveis, pra isto futuras pesquisas deverão focar em populações mais semelhantes (idade, sexo e escolaridade) bem como um uso de testes padronizados e amplos ao máximo de domínios cognitivos possíveis. O uso clínico do Teste Auditivo-Verbal de Rey (RAVLT) é recomendado para se investigar o padrão subcortical x cortical das demências e o possível diferencial entre HAND e DA. O RAVLT é um teste validado e normatizado para a população brasileira (Malloy-Diniz et al. 2009), de fácil aplicação para profissionais da neuropsicologia treinados, com fácil adaptação em populações de baixa escolaridade.

Referências:

1. Alkali NH, Bwala SA, Nyandaiti YW, Danesi MA. (2013). NeuroAIDS in sub-Saharan Africa: a clinical review. *Ann Afr Med*. 12(1):1-10.
2. Christo PP, Géo LAL, Antunes CMF. (2013). Neurocognitive performance in patients with AIDS in Brazil: a case-control study. *Clinical Neuropsychiatry*.10, 2, 107-110.
3. Cohen RA, Harezlak J, Gongvatana A, Buchthal S, Schifitto G, Clark U, Paul R, Taylor M, Thompson P, Tate D, Alger J, Brown M, Zhong J, Campbell T, Singer E, Daar E, McMahon D, Tso Y, Yiannoutsos CT, Navia B; HIV Neuroimaging Consortium. (2010). Cerebral metabolite abnormalities in human immunodeficiency virus are associated with cortical and subcortical volumes. *J Neurovirol*. 16(6):435-44.

4. de Almeida SM, Ribeiro CE, de Pereira AP, Badiee J, Cherner M, Smith D, Maich I, Raboni SM, Rotta I, Barbosa FJ, Heaton RK, Umlauf A, Ellis RJ. (2013). Neurocognitive impairment in HIV-1 clade C- versus B-infected individuals in Southern Brazil. *J Neurovirol*. 19(6):550-6.
5. De Ronchi D, Fratiglioni L, Rucci P, Paternicò A, Graziani S, Dalmonte E. (1998). The effect of education on dementia occurrence in an Italian population with middle to high socioeconomic status. *Neurology*. 50(5):1231-8.
6. Delis DC, Peavy G, Heaton R, Butters N, Salmon DP, Taylor M, et al. (1995). Do patients with HIV-associated minor cognitive/motor disorder exhibit a "subcortical" memory profile? Evidence using the California Verbal Learning Test. *Assessment.* 2, 151–165.
7. Joseph J, Achim CL, Boivin MJ, Brew BJ, Clifford DB, Colosi DA, Ellis RJ, Heaton RK, Gallo-Diop A, Grant I, Kanmogne GD, Kumar M, Letendre S, Marcotte TD, Nath A, Pardo CA, Paul RH, Pulliam L, Robertson K, Royal W 3rd, Sacktor N, Sithinamsuwan P, Smith DM, Valcour V, Wigdahl B, Wood C. (2013). Global NeuroAIDS roundtable. *J Neurovirol*. 19(1):1-9.
8. Malloy-Diniz LF, Lasmar VAP, Gazinelli R, Fuentes D, Salgado JV. (2009) The Rey auditory-verbal learning test: applicability for the Brazilian elderly population. *Revista Brasileira de Psiquiatria*. v. 29, n. 4, p. 324-329.
9. McArthur JC. (2004). HIV dementia: an evolving disease. *J Neuroimmunol*. 157(1-2):3-10.
10. Price RW, Yiannoutsos CT, Clifford DB et al. (1999). Neurological outcomes in late HIV infection: adverse impact of neurological impairmentr on survival and protective effect of antiviral therapy. *AIDS*. 13:1677-1685

11. Rodrigues RA, Oliveira RL, Grinsztejn B, Silva MT. (2013). Validity of the International HIV dementia scale in Brazil. *Arq Neuropsiquiatr*. 71(6):376-9.
12. Sackor NC, BacellarH, Hoover DR et al. (1996). Psychomotor slowing in HIV infection: a predictor of dementia, AIDS and death. *J Neurovirol*. 2:404-410.
13. Sadek JR, Johnson SA, White DA, Salmon DP, Taylor KI, Delapena JH, Paulsen JS, Heaton RK, Grant I. (2004). Retrograde amnesia in dementia: comparison of HIV-associated dementia, Alzheimer's disease, and Huntington's disease. *Neuropsychology*.18(4):692-9.
14. Smurzynski M, Wu K, Letendre S, et al. (2011). Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. *AIDS* 25(3):357-365.
15. UNAIDS/WHO - Boletim epidemiológico AIDS-DST Ano VIII No1 publicado 28/11/2011. http://www.aids.gov.br/publicacao/2011/boletim_epidemiologico_2011.
16. Woods SP, Moore DJ, Weber E, Grant I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychol Rev*.;19(2):152-68.
17. Woods SP, Moran LM, Carey CL, Dawson MS, Iudicello JE, Gibson S, Grant I, Atkinson JH; HIV Neurobehavioral Research Center Group. (2008). Prospective memory in HIV infection: Is “remembering to remember” a unique predictor of self-reported medication management? *Arch Clin Neuropsychol.* ;23(3):257-70.
18. Xu J, Ikezu T. (2009). The comorbidity of HIV-associated neurocognitive disorders and Alzheimer’s disease: a foreseeable medical challenge in post-HAART era. *J Neuroimmune Pharmacol.* 4(2): 200–212.

Anexo 1 – Artigo publicado com os dados básicos da dissertação

Neurocognitive Performance in Patients with AIDS in Brazil: a case-control study.

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Abstract:

Objectives: 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. Methods: 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. Conclusion: 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.

Keywords:

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 ganglia1. 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[2].

Chronic HIV-1 infection can result in neurodegenerative disease, overall termed NeuroAids. The expression of this process includes neurocognitive impairments en several domains[3].

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[4].

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[5].

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 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[8]); language: phonemic verbal fluency (FAS test[9]) and semantic verbal fluency (animal categories); non-verbal fluency (total number of drawings in the 5-point test[10]); 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* [11] and Rey Complex Figure[12]), fine motor coordination (Nine Hole Peg Test[13]) 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[14], 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.

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 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 [5].

As has been described [4], 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 [15]. Prospective memory deficits provides incremental ecological in predicting general IADL declines and medication mismanagement[4].

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.

Attachment

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

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.

REFERENCES

1-Navia BA, Jordan BD, Price R W (1986). The AIDS dementia complex, I: clinical features. A*nnals of Neurology* 19, 517-524.

2- Aylward EH, Henderer JD, McArthur JC, Brettschneider PD, Harris GJ, Barta PE, Pearlson GD (1993) . Reduced basal ganglia volume in HIV-1-associated dementia: results from quantitative neuroimaging. *Neurology* 43,10, 2099-104.

3- Shapshak P, Kangueane P, Fujimura RK et al (2011). Editorial NeuroAIDS review. *Aids* 25, 125-141.

4- Woods SP, Moore DJ, Weber E, Grant I (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychol Rev*, 19,2 152-68.

5- Christo PP. Cognitive alterations associated with HIV-1 infection and AIDS (2010). *Rev Assoc Med Bras* 56,2, 242-7.

6- Regard, M (1981). Cognitive rigidity and flexibility: A neuropsychological study. *Unpublished Ph.D. dissertation*, University of Victoria.

7- Reitan, RM (1955). The relation of the Trail Making Test to organic brain damage. *Journal of Consulting Psychology*, 19, 393–394.

8- Wechsler, D (1991, 3rd Ed.). Wechsler Intelligence Scale for Children (WISC-III): Manual. San Antonio: The Psychological Corporation.

9- Gladsjo, JA, Schuman, CC, Evans, JD, Peavy, GM,Miller, SW, & Heaton, RK (1999). Norms for letter and category fluency: Demographic corrections for age, education, and ethnicity. *Assessment*, 6, 147–178.

10- Regard, M, Strauss, E, & Knapp, P (1982). Children's production of verbal and nonverbal fluency tasks. *Perceptual and Motor Skills*, 55, 839–844.

11- Malloy-Diniz, LF, Lasmar, VAP, Gazinelli, RS, Fuentes, D, Salgado, JV (2009). The Rey auditory-verbal learning test: applicability for the Brazilian elderly population. *Revista Brasileira de Psiquiatria* 2009 29,4,324-329.

12- Jamus, DR, Mader, MJ, (2005). A Figura Complexa de Rey e Seu Papel na Avaliação Neuropsicológica. *J Epilepsy Clin Neurophysiol*, 11,4,193-198.

13- Rodrigues JL, Ferreira FO, Haase VG (2008). Perfil do desempenho motor e cognitivo na idade adulta e velhice. *Gerais: Revista Interinstitucional de Psicologia* 1, 20-33.

14- Bertolucci PHF, Brucki SMD, Campacci SR, Juliano Y (1994). O Mini-exame do Estado Mental em uma população geral. Impacto da escolaridade. *Arq. Neuropsiquiatr.*, 52:1-7.

15- Heaton RK, Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bentley H, McCutchan JA, Reicks C, Grant I; HNRC Group (2004). The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc*. 10,3,317-31.

Anexo 2 – Análise de curva ROC sobre a capacidade de discriminação dos testes cognitivos

Area Under the Curve

Test Result Variable(s)	Area
paced	,809
fl.cinco	,805
paced1	,742
codigos	,716
figura_r	,708
figura_2	,686
figura_1	,679
fl.part	,675
fl.alime	,666
d_gitos	,665
f.a.s	,630
ravlt_to	,587
ravlt_a7	,584
ravlt__1	,570
fl.anima	,561
ravlt__a	,510
Nine_htp	,426
ravlt_ra	,414
stroop_3	,407
stroop_1	,352
trilhasa	,350
trilhasb	,310
stroop_2	,308