ORIGINAL ARTICLE

Memory Performance in HIV/AIDS - A Prospective Case Control Study

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ABSTRACT: ***Background:*** Memory impairment, usually impaired retrieval of information, has been described in HIV/AIDS, especially among those with severe illness. Neuro-cognitive disturbances in HIV/AIDS have been linked to poor quality of life and medication adherence. This prospective, case-control study was designed to assess the verbal and non-verbal memory as well as the attention abilities of Nigerian Africans with HIV/AIDS and correlate their performances with their CD4+ T lymphocytes (CD4+) counts. ***Methods:*** A total of 288 randomly selected subjects, comprising 96 HIV-positive symptomatic patients, 96 HIV-positive asymptomatic patients and 96 HIV-negative controls, participated in the study. The subjects were age-, sex-, and level of education matched. The Recognition Memory Test and Choice Reaction Time tasks, components of the computer-assisted neuropsychological tests battery- the Iron Psychology 'FePsy' were used for cognitive assessments. ***Results:*** The mean memory scores of the HIV-positive asymptomatic subjects did not differ significantly from the controls ($p>0.05$) but the HIV-positive symptomatic subjects' scores were significantly lower than the controls ($p<0.05$). Both HIV-positive groups had psychomotor slowing and impaired attention ($p<0.05$). The HIV-positive subjects with CD4+ counts <200/µl and between 200 and 499/µl had significant memory impairment ($p<0.001$ and $p<0.001$ respectively) but there was no significant impairment among those with count ≥500/µl. Impaired ability for sustained attention was however present irrespective of the CD4+ level relative to controls ($p<0.001$). ***Conclusions:*** We concluded that there was no significant memory disturbance among HIV-positive asymptomatic subjects despite the presence of impaired attention and psychomotor slowing, and that the severity of immune suppression (as indicated by the CD4+ T lymphocytes count) is a strong determinant of cognitive decline in HIV/AIDS.

RÉSUMÉ: Étude prospective cas-témoin du fonctionnement mnésique chez les patients atteints du VIH/SIDA. ***Contexte :*** Une atteinte de la mémoire, habituellement de la récupération de l'information, a été décrite chez les patients atteints du VIH/SIDA, spécialement chez ceux dont la maladie est sévère. Les perturbations neuro-cognitives dans le VIH/SIDA ont été associées à une faible qualité de vie et de fidélité à la médication. Cette étude prospective cas-témoin a été conçue dans le but d'évaluer la mémoire verbale et non verbale ainsi que l'attention chez des Africains Nigériens atteints du VIH/SIDA et d'évaluer s'il existe une corrélation avec le décompte des lymphocytes T CD4+ (CD4+). ***Méthodes :*** 288 sujets choisis au hasard, soit 96 patients VIH-positifs symptomatiques, 96 patients VIH-positifs asymptomatiques et 96 témoins VIH-négatifs ont participé à l'étude. Les sujets ont été appariés pour l'âge, le sexe et le niveau de scolarité. L'évaluation cognitive a été effectuée au moyen du Recognition Memory Test (RMT) et du Choice Reaction Time Tasks, qui font partie d'une batterie de tests neuropsychologiques informatisés, le Iron Psychology « FePsy ». ***Résultats :*** Les scores mnésiques moyens des sujets asymptomatiques VIH-positifs n'étaient pas significativement différents de ceux des témoins ($p > 0,05$). Cependant, les scores des sujets VIH-positifs symptomatiques étaient significativement plus bas que ceux des témoins ($p < 0,05$). Les deux groupes de patients VIH-positifs avaient un ralentissement psychomoteur et un déficit d'attention ($p < 0,05$). Les sujets VIH-positifs dont le décompte CD4+ était inférieur à 200/Ìl et entre 200 et 499/Ìl avaient une atteinte mnésique significative ($p < 0,001$ et $p < 0,001$ respectivement). Il n'existait pas d'atteinte significative chez ceux dont le décompte était ? 500/Ìl. Cependant, ils avaient un déficit de l'attention soutenue par rapport aux témoins ($p < 0,001$), quel que soit leur décompte CD4+. ***Conclusions :*** Il n'y a pas de perturbation significative de la mémoire chez les sujets VIH-positifs asymptomatiques, malgré la présence d'un déficit de l'attention et d'un ralentissement psychomoteur. La sévérité de la suppression immunitaire (basée sur le décompte des lymphocytes T CD4+) est un déterminant puissant du déclin cognitif chez les sujets atteints du VIH/SIDA.

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Neuropsychological impairments in HIV/AIDS have been extensively researched and reported in developed countries, usually reflecting the prominence of initial sub-cortical involvement and characterized by memory loss (usually impaired retrieval), general slowing of psychomotor speed and thought processes and impaired manipulation of acquired knowledge.[1,2] Memory impairment, both verbal and non-verbal, is characteristic of HIV-associated dementia.[3]

During the early years of the HIV epidemic, cognitive symptoms were thought to be common even during the initial medically asymptomatic stages of the infection.[2] The HIV-associated dementia commonly occurs during advanced stages of

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infection and in the setting of severe immuno-suppression[4,5] but there are immuno-suppressed HIV-positive patients who are not demented.[6] However more recent studies have shown the presence of a less severe antecedent condition, minor cognitive-motor disorder (MCMD), which can occur during stages of comparative immunostability. Before the introduction of highly active anti-retroviral therapy (HAART), a dementia syndrome developed in approximately 15% to 20% of patients with advanced HIV disease.[6] However, in about 1-3% of patients, dementia was evident before the diagnosis was made.[3] Neuro-cognitive impairment may affect quality of life in patients with HIV/AIDS, especially those with severe impairments. Identifying this complication will permit the use of additional treatment to help patients compensate for deficits in functioning.

The statistics of HIV/AIDS in sub-Saharan Africa is alarming, with 90 percent of 36.1 million HIV/AIDS patients living in developing countries. Of these, 25.3 million are in sub-Saharan Africa with an adult prevalence rate of 8.8 percent.[7,8]

The availability of HAART has resulted in modest reduction of mortality from this disease in Nigerians, hence more patients are likely to live longer and care givers would have to deal with increasing prevalence of subtle and major cognitive complaints among survivors.

There has been no information on the cognitive functioning of Nigerians with HIV/AIDS using objective neuro-psychological tools. This prospective case control study assessed the memory performance and sustained attention of our patients and correlated these with their CD4+T lymphocytes (CD4+) levels to determine the impact on their performances.

Patients and Methods

A total of 192 patients (with positive ELISA test to HIV) were randomly recruited from a total of 720 newly diagnosed patients attending the HIV/AIDS clinics of the University Teaching Hospital, Benin City, Nigeria over a six month period (January – June 2004). The study population comprised antiretroviral treatment-naïve 96 HIV-positive asymptomatic and 96 symptomatic AIDS subjects. The latter were categorized as symptomatic based on the presence of at least one of these symptoms; persistent pyrexia (more than four weeks duration), recurrent diarrhea (more than four weeks duration), unexplained weight loss (more than 10% of previous weight) and generalized skin rash. Ninety-six HIV-negative healthy volunteers were selected randomly from among hospital staff members in the outpatient departments and antenatal clinics as controls. All the subjects and controls had their CD_4 levels measured with manual and automated flow cytometry ((CyFlow™; Partec GmbH, Munster, Germany). All the subjects were matched for age, sex and level of education. Informed consents were obtained from the subjects and controls, and approval to undertake study was granted by the Hospital Ethics Committee.

All subjects were interviewed using a basic questionnaire by one of the authors (FEO) to obtain demographic variables. The inclusion criteria included HIV seropositivity – asymptomatic individuals, above 18 years of age and symptomatic AIDS patients, above 18 years of age. The exclusion criteria included subjects less than 18 years of age, patients already on anti-retroviral therapy, and patients with co-morbidity (diabetes mellitus, hypertension epilepsy, and associated intracranial disorders e.g. brain tumor, and other metabolic diseases), those with opportunistic infections, those with an inconclusive diagnosis, major axis 1 psychiatric illness, presence of clinical signs of cardiac failure, alcohol intake above 120 gm/week or 13 units/week, history of previous head injury with loss of consciousness and patients on anti- cholinergic medications.

Cognitive testing

The administration of tests was done with the FePsy computerized neuropsychological test battery created and designed by the department of Psychology of Het Instituut voor Epilepsiebestrijding, Netherlands (Stichting Epilepsie Instellingen Nederland, Achterweg 5, 2103 SW Heemstede, Netherlands).[9,10] The Iron Psychology, acronym 'FePsy' is a computer-assisted neuropsychological instrument which consists of reaction time tasks (simple and choice), recognition memory tests, visual scanning task, seashore rhythm test, abstraction task (similar to Wisconsin card sorting task) and Corsi block task. It has been used in our center and western European countries extensively. It has been validated among Nigerians and there are normative data for comparison with education levels, sex and age groups.

Test presentation and response registration were controlled by a microcomputer, but one of the authors (OAO) was always present to adjust instructions to the individual performance level of the patients. The cognitive assessment was blind as the author (OAO) was not aware of the patients' HIV status.

It is pertinent to mention that the subjects need not be computer literate to perform the tests, as they only need to carry out instructions as they relate to each test. The test is level of education-based as the tests for primary (6 years of schooling) differ from secondary (between 7 and 11 years of schooling) and tertiary (more than 11 years of schooling) levels of education. Language does not affect performance. The tests were administered in a reasonably quiet, well-lit room at room temperature of between 22°C and 25°C, between the hours of 10:00 and 13:00 each day of testing with the subject sitting comfortably at a distance of 40 to 60 centimetres from the visual display screen. Care was taken to ensure sufficient brightness and contrast of screen and sufficient sound level of the speaker.

Memory was assessed using the Recognition Memory test.[11] The test involves the use of study items which consist of 3 or 4 figures (for the visual, non-verbal memory test) and 4 or 6 words (for the verbal memory test) which are presented simultaneously. The task is divided into a study phase in which the material to be remembered is presented and a test phase in which recognition is tested. A delay of two seconds is allowed between study phase and the test phase. In the test phase, the figures or words are presented again and the target item has to be recognized. Patients with primary school education were tested using 3 figures and 4 words, while those with secondary and post-secondary education were tested using 4 figures and 6 words. Each subject had a session of 20 trials after a practice phase of 2 trials. The results were calculated as percentage of correct responses. The evaluation of the recognition task was performed in the context of the short-term memory function. The detail of this test has been described earlier.[12]

Attention was assessed by the choice reaction test which involves the display of either a red or a green half square-inch

block in a random sequence in either the left or right half of a screen. The testee is asked to push one of two buttons on either side of a keyboard, corresponding to the position of the coloured block on the screen. The test is 'self-paced' and continuous, which implies that a response is immediately followed by substitution of another block in either the same or in the opposite position. After an initial practice of 10 stimuli, 60 stimuli are presented. The results show accuracy and speed (in milliseconds) of responses. Accuracy or sensitivity is expressed as fraction of correct responses to the total responses. Evaluation is carried out in the context of speed of information processing (psychomotor speed) and attention.

The average choice reaction times for normal Nigerians are 422±92.3 milliseconds (with accuracy or sensitivity of 0.85±0.14) age range 18 – 45 years, while the mean memory performances are 85.8% and 53.6% for the verbal and non-verbal memory respectively.

Statistical analysis of the data was done with the aid of Epi Info 2000 software. The means of the performances of the patients and controls were tested for significance with 2-way analysis of variance (ANOVA), the risk of developing cognitive impairment was determined using odds ratio and correlation of CD4+ counts with cognitive scores was assessed using the Pearson correlation coefficient. The level of significance was taken at $p<0.05$.

Results

All the 288 subjects, made up of 96 randomly selected patients with symptomatic AIDS, 96 randomly selected patients with asymptomatic HIV infection and 96 HIV –negative controls, completed the study. These three categories of subjects comprised 48 males and 48 females. The mean ages were 32.9± 8.0 years, 31.5±6.7 years and 33.6±7.1 years for the controls, asymptomatic HIV positive and symptomatic AIDS subjects respectively ($p = 0.13$). The means of the CD4+ counts for the controls, HIV-positive asymptomatic and symptomatic subjects were 682±44, 284±62 and 142±36 respectively ($p<0.05$). The details of demographic information are presented in Table 1.

The mean performances of the asymptomatic HIV positive and symptomatic AIDS patients in the Recognition Memory testing (verbal and visual, non –verbal memory) were compared with the controls. The details are outlined in Table 2.

The choice reaction time, a measure of the attention ability and psychomotor speed of the patients, revealed significant differences in time taken (psycho-motor determinant) to perform the tasks ($p<0.05$) and the sensitivity of the HIV-positive patients (attention ability) compared to the controls ($p<0.05$) see Table 3.

The cognitive scores of the patients were correlated with their corresponding CD4+ levels. The verbal memory scores of 72.1% ($p <0.0001$) of patients with CD4+ count between 200 and 499/µl and 79.6% ($p<0.0001$) of patients with CD4+ count <200/µl were significantly lower than controls whereas among those with CD4+ count > 500/µl only 20.2% had lower scores ($p>0.05$). For the non-verbal memory scores, 68.9% ($p<0.0001$) of patients with CD4+ count between 200 and 499/µl and 99% ($p<0.0001$) of patients with CD4+ count less than 200/µl had lower scores than controls. The scores of patients with CD4+ level greater than 500/µl were also significantly different from the controls, 50% of them had lower scores ($p<0.05$).

The odds ratios for the various CD4+ levels are outlined in Table 2. The risk of developing memory impairments increased

Table 1: Demographic information of patients and controls

	Controls (N=96)	Asymptomatic HIV-positive patients (N=96)	Symptomatic AIDS patients (N=96)
Sex			
Male	48 (50%)	48 (50%)	48 (50%)
Female	48 (50%)	48 (50%)	48 (50%)
Age (years)			
20-29	40 (41.7%)	43 (44.8%)	40 (41.7%)
30-39	34 (35.4%)	37 (38.5%)	34 (35.4%)
40-49	21 (21.9%)	16 (16.7%)	21 (21.9%)
≥50	1 (1.0%)	0.0 (0%)	1 (1.0%)
Level of Education			
Primary[a]	48 (50%)	48 (50%)	48 (50%)
Secondary[b]	36 (37.5%)	36 (37.5%)	36 (37.5%)
Tertiary[c]	12 (12.5%)	12 (12.5%)	12 (12.5%)

[a] - 6 years of schooling, [b] - between 7 and 11 years of schooling, [c] - more than 11 years of schooling

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Table 2: Means of memory performance and correlation with CD_4 count

Categories of subjects	Recognition memory test (means of % correct responses)			
	Verbal memory (words)		Non-verbal memory (figures)	
Controls	81.5±19.3		65.2±20.2	
HIV-positive asymptomatic	72.1±16.4	p >0.05	51.9±17.9	p > 0.05
HIV-positive symptomatic	51.7±21.4	p < 0.001	31.3±19.2	p < 0.05
		% with abnormal performance		% with abnormal performance
CD4+ levels				
controls	81.5±19.4	18.5%	65.2±20.2	32.5%
>500	82.3±18.3	20.2%(p=0.86, OR 1.14; 95% CI 0.56-2.32)	65.8±19.8	50%(p=0.02, OR 2.10; 95% CI 1.17-3.77)
200-499	71.5±21.3	72.1%(p<0.0001, OR 11.07; 95% CI 5.62-21.83)	52.3±21.4	68.9%(p<0.0001, OR 4.61; 95% CI 2.51-8.47)
<200	51.7±22.8	79.6% (p<0.0001, OR 17.56; 95% CI 8.57-35.99)	31.3±21.3	99%)p<0.0001, OR 199.19; 95% CI 26.51-1496.6

with increasing severity of immuno-suppression. The subjects with CD4+ counts less than 500/µl had higher odd ratios than those with CD4+ counts greater than 500/µl.

The sensitivity, a measure of attention ability, was reduced in 50.5% of patients with CD4+ count > 500 cells/mm^3 compared to controls (p<0.001) and 62.5% of those with count between 200 and 499 cells/mm^3 (p< 0.001). Of patients with CD4+ count <200 cells/mm^3, 83.7% had reduced sensitivity (P<0.001) see table 3.

This interesting observation indicated significant impairment in attention of patients with HIV/AIDS irrespective of the degree of immuno-suppression (i.e. the CD4+T lymphocytes count).

Discussion

Despite the introduction of highly active anti-retroviral therapy, the prevalence of memory and other cognitive symptoms in HIV/AIDS remains steady although the incidence of HIV-related dementia has decreased.[13] Memory disturbance is the most distressing of the neuro-cognitive disturbances because of its impact on daily living, coping with employment,[14] driving,[15,16] medication regimen[17] and, detrimental effect on quality of life in general. With improvement in survival due to HAART, the understanding of the epidemiology and typology of these neuro-cognitive impairments will improve early diagnostic assessment and intervention. Depression can often result in subjective symptoms but rarely causes objective cognitive impairment.[2]

The cognitive profile of patients who present with HIV-related dementia is similar to that of patients who have other disorders with predominantly sub-cortical disease.[3] In the early stages, forgetfulness, slowing of response and difficulties in multitasking are evident. In contrast, language, arithmetic calculations, reading and other cortical functions are relatively preserved.[2,4]

Memory impairments have been demonstrated in several studies, especially affecting verbal memory.[1,2,18,19] Our study confirmed the presence of memory impairments, suggesting retrieval deficits inferred by impaired memory recognition, in patients with symptomatic HIV infection but the difference between the asymptomatic subjects and controls was insignificant. This observation is in keeping with findings of other workers.[20-23] There have been contrary reports however stating the presence of memory dysfunction even in asymptomatic HIV-positive subjects.[2,23,24]

This inconsistent observation has been explained based on the complexity of the neuropsychological test batteries (i.e. task difficulty) and sample sizes used in various studies. Recall tasks are more tasking than recognition tasks, and this may explain the absence of memory impairment in the asymptomatic HIV-positive group. Newman et al[25] showed a peculiar inverse

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Table 3: Mean of choice reaction time scores and correlation with CD_4

Cognitive tests	Controls (n=96)	Asymptomatic HIV-positive (n=96)	Symptomatic HIV-positive (n=96)	
Mean CD_4 (/mm^3)	682±44	284±62 (p<0.001)	142±36 (p<0.001)	
Mean age (years)	32.9±8.0	31.5±6.7 (p=0.21)	33.6—7.1 (p=0.33)	
Binary Choice Reaction Time taken (millisecond)	432.8±170.4	557.1±126.3 (p<0.001)	665.2±128.3 (p<0.001)	
Sensitivity (% correct responses)	95.1±5.2	90.0±4.5 (p=0.013)	85.1±6.2 (p<0.001)	
CD4+ levels	time taken (millisec)	% prolonged time	Sensitivity (% correct)	% impaired sensitivity
Controls	432.8±170.4	21.4	95.1±5.2	18.5
>500 count	553±173.2	27.6 (p=0.41, OR 1.40 95% CI 0.72-2.70)	93.1±5.9	50.5 (p<0.001, OR 4.52 95% CI 2.36-8.66)
200-499 count	576.6±170.4	38.5 (p=0.02, OR 2.24 95% CI 1.19-4.23	90.7±6.2	62.5 (p<0.001, OR 7.22 95% CI 3.74-13.95)
<200 count	665.2±153.1	82.7 (p<0.001, OR 16.60 95% CI 8.13-33.87	85.1±7.6	83.7 (p<0.001, OR 23.40 95% CI 11.02-49.67

relationship between the size of study and the likelihood of detecting a difference in neuropsychological performance. There are several reports that have demonstrated the superiority of computerized neuro-cognitive assessment over the traditional psychometric analysis as the former readily detect subtle cognitive dysfunction.[26] The same conclusion was drawn by White[27] who stated that a major factor in whether impairment was detected by a study had to do with the comprehensiveness of the neuropsychological assessment. Notwithstanding, most observers agree that symptomatic HIV infection is accompanied by an increased rate of neuropsychological impairments. The significant impairment of sustained attention may be responsible for the memory disturbance in the symptomatic patients. Both HIV-positive groups had significant psychomotor slowing corroborating findings from other studies.[28,29]

Extensive research has also proved that cognitive decline is more likely in the setting of severe immuno-suppression or significant plasma or central nervous system (CNS) viral load.[1-3,19-23,29,30] This was consistent with the results of our study. The risk of developing verbal memory impairment increased with declining CD4+ counts as patients with less than 200/µl counts were 17 times more likely to have impairment when compared with sero-negative controls while those with counts between 200 and 499/µl were 11 times more likely. Those with counts greater than 500/µl did not differ significantly from controls. The same trend was observed for visual (non-verbal) memory, a more difficult task, though the subjects with greater than 500/µl counts were twice as likely to have visual memory impairment in this regard. This suggests that more complex tasks requiring memory functioning are likely to reveal cognitive decline in HIV/AIDS.

The mechanisms responsible for HIV-associated neuro-psychological impairments have not simply been correlated with viral load in the brain but also with cytokines excess affirming that its pathogenesis is dominated by indirect neuronal damage. Such substances like neopterin (which enhances the reactivity of reactive oxygen and chloride species, and susceptibility to TNF-α - induced apoptosis), β2 macroglobulin and quinolinic acid (a neuronal excito-toxin that acts at the NMDA receptor) may directly cause neuronal disturbance and dysfunction. Platelet activating factor (PAF) facilitates glutamate release, resulting in cell death. All these effects culminate in significant neuro-degeneration which has been demonstrated using neuro-imaging studies.[28,31,32] The HIV envelope protein gp120 also induces neurotoxicity by increasing intracellular calcium.[33]

Numerous cross-sectional and longitudinal studies have proved the benefits of HAART regimens in the management of HIV-associated dementia and neuro-cognitive impairments.[34,35] Our subjects were untreated and it is expected that with the administration of HAART there will be improvement in their

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cognitive abilities. There is need for an interventional study that will assess the effect of HAART on cognitive impairments in Nigerian patients with HIV/AIDS.

This study confirmed the presence of significant memory and attention impairments in symptomatic HIV infection and the worsening of cognitive performances with progression of disease and in the face of severe immune suppression. The memory abilities of the asymptomatic HIV-positive subjects were comparable with the HIV-negative controls despite impaired attention.

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