



Cognitive functions in newly diagnosed patients with HIV infection in a tertiary health facility: Assessment using community screening interview for dementia

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ABSTRACT

Introduction: Neurocognitive dysfunction is a detrimental complication of HIV infection. In this study we attempt to characterize the pattern of cognitive dysfunction in a sample of Nigerian patients with newly diagnosed HIV infection.

Methods: We conducted a prospective study in which 50 patients with newly diagnosed HIV infection were studied along with 50 normal control subjects. The participants were evaluated with the medical history, general, physical and neurological examination. Laboratory evaluation and chest X-Ray were done for all patients. The Community Screening Interview for Dementia (CSID) questionnaire was administered to all the study participants.

Results: About 70% of the patients were in advanced disease stage. The mean age (SD) of the patients and controls in years were 36.44 ± 8.22 and 35.40 ± 11.53 respectively. More than half (56%) of the patients had secondary level of education (12 years of education). About 20% of the patients had severe neurocognitive impairment while 48% had minor neurocognitive disorder. The patients with HIV infection performed poorly in the domains of language, memory, orientation, attention/calculation and praxis relative to controls ($p < 0.05$). There were no significant effect of gender, age, sex and level of education on cognitive functions in the patients ($p > 0.05$) but the presence of opportunistic infections had negative impact on the performances on orientation and total CSID scores in the patients with HIV infection ($p < 0.05$).

Conclusion: Patients with newly diagnosed HIV infection have poor cognitive functions when compared to normal controls and some presence of opportunistic infections in the patient is a significant risk factor for cognitive impairment.

1. Introduction

Human Immunodeficiency Virus (HIV) infection is a major cause of neurocognitive dysfunction in the world [1]. A recent data suggested that about 36.9 million people in the world were infected with HIV infection and that 70% of this population live in sub-Saharan Africa [2]. The cognitive impairment described in patients with HIV infection usually affected the domain of memory, attention/concentration, psychomotor speed, praxis and in advanced stages language and orientation may be affected [3,4,5]. The HIV associated neurocognitive disorder (HAND) is the term used to describe the cognitive impairment (NCI) that patients with HIV infection exhibit [6,7]. Asymptomatic

neurocognitive impairment (ANI) is the term used to describe a situation where patients with HIV infection exhibit cognitive deficits that are subclinical but could only be detected by neuropsychological test. The HIV associated dementia (HAD) is the most severe form of NCI in HIV patients and activities of daily living is impaired in the patients while the minor neurocognitive disorder (MND) is in between ANI and HAD in severity [7]. Timely detection of NCI in patients with HIV infection is very crucial as HAND could affect patients activities of daily living such as medication adherence employment, driving and so on.

The evaluation of cognitive function in HIV patients have been done previously with “Gold standard” neuropsychological tools which usually give a valid and reliable results [8,9,10]. These

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neuropsychological test batteries are usually not available in developing countries and simple, inexpensive, universally available, brief, screening tools are desirable for evaluation of NCI in patients with HIV infection in developing countries. Various screening tools that have been used in the past for HIV patients included Mini Mental State Examination (MMSE) scale, Montreal Cognitive Assessment scale, HIV Dementia scale, International HIV Dementia Scale, Simioni Symptoms Questionnaire, Cognitive Assessment Tool – rapid version and so on [11]. In this study, we used a simple, validated Community Screening Interview for Dementia (CSID) to evaluate the cognitive functions in patients with HIV function in our centre and also in addition evaluated the relationship between some clinical/socio demographic and laboratory variables with cognitive function in these patients.

2. Methods

This was a prospective study in which fifty patients with HIV infection were studied along with fifty normal control subjects. The study was carried out at Federal Medical Centre, Owo, Ondo State, Nigeria. The hospital was selected by the Federal Government for free management of Patients with HIV infection.

The inclusion criteria were age > 16 years, seropositivity to HIV infection, and patients must not be on anti-retroviral therapy (ART). The exclusion criteria were the presence of co-morbidities that could cause cognitive impairment in the patients such as Parkinson's disease, epilepsy, metabolic diseases, brain tumor, current use of psychoactive drugs, drug abuse, use of anticholinergic medications, previous head trauma with loss of consciousness. Other exclusion criteria were alcohol intake > 13 units/week, severe anaemia (PCV < 20%) and severe functional impairment (Karnofsky performance < 50%). Known psychiatric patients or those who showed clinical features of major psychiatric disorders such as major depression, schizophrenia, mania and so on were also excluded from the study.

The study participants had general physical and neurological examination done. The patients were staged clinically using World Health Organization staging system [12].

The presence of opportunistic infections were identified in the patients with the aid of chest x-ray, sputum microbiological testing and positive response to empirical therapy with anti-toxoplasmosis drug was taken as evidence of toxoplasmosis infection. The renal function tests and haematological work-up were done in all the patients while HIV serological testing were done with Enzyme linked immunosorbent assay (ELISA) and CD4 cell count was done by automated flow cytometry method.

2.1. Cognitive function evaluation

All the study participants had cognitive function assessment done with the aid of Community Screening Interview for Dementia (CSID) as adapted for Nigerians. The CSID is a 48 item-questionnaire that have been used in different developing countries and was found to be suitable for assessment of cognitive function. The result obtained from a study [13] showed that CSID is unaffected by culture and level of education. The CSID have been validated in several Nigerian studies on Alzheimers disease [14,15], epilepsy [16], liver cirrhosis [17] and HIV patients [18,19]. The CSID was shown to have impressive screening quality in a Nigerian Study [16].

The CSID is a simple “paper and pen” instrument that evaluate the following cognitive domains language (tasks assessing naming, comprehension, motor response, naming fluency, definition, and repetition) memory (tasks assessing, Recall, registration and remote memory), attention/calculation, orientation (time and place) and praxis (copying). The CSID is administered to the study participants by the neurologist in a quiet and well-lit room usually in the morning time to ensure that the participants were not fatigued and the scores obtained were documented.

2.2. Statistical analysis

The demographic characteristics variables between patients with HIV infection and controls were analyzed with Chi square (χ^2) test. The mean scores of the various domain of the CSID were compared between the patients and controls using the student's *t*-test. The relationship between the various clinical/socio-demographic variables and domains of the cognitive function were analyzed using the student *t*-test or one-way analyses of variance (ANOVA) as appropriate. The effects sizes of all these analyses were calculated using Cohen's *d* or η^2 as appropriate $d = 0.2$ – 0.5 – small effect size, 0.5 – 0.7 – medium effect size, ≥ 0.8 – large effect size. $\eta^2 = 0.01$ – 0.059 – small effect size, 0.059 – 0.138 – medium effect size, ≥ 0.138 –large effect size. Level of statistical significance was taken as $p < 0.05$.

3. Results

One hundred and thirty-one participants were initially recruited for the study but thirty-one participants (20 patients with HIV infection and 11 controls) were excluded from the study because of incomplete data and unwillingness to participate in the study. Fifty patients with HIV infection and fifty normal controls participated in the study. The mean age of the patients with HIV infection was 36.44 ± 8.22 years while that of the normal control was 35.50 ± 11.53 years ($p > 0.05$). The other socio-demographic characteristics of the study participant were as shown in Table 1.

Table 2 showed the frequency distribution of the clinical variables of the HIV positive patients in this study.

Table 3 showed the proportion of the participants that have severe neurocognitive impairment which is defined as any total CSID score which less than the mean total CSID score of the controls minus 2 standard deviation. In this study about 20% of patients with HIV and none of the control subject had severe NCI ($p < 0.001$).

Participants with minor neurocognitive disorder (MNCD) are defined as participants with total CSID score that were in the range between the 2 standard deviation and 1 standard deviation of the control mean. In this study, 48% of the patients with HIV infection and 36% of the controls had MNCD ($p < 0.05$). This is illustrated in Table 3.

The comparison of the cognitive function between the patients with HIV infection and normal control were as shown in Table 4. In this Table, the patients performed significantly poorer in all the domains of cognitive functions of the CSID instrument when compared to normal controls ($p < 0.05$).

Table 5 showed the relationship between having opportunistic infections (OIs) in HIV infected patients and their cognitive performances. Opportunistic infections was associated with impairment in memory

Table 1
Socio-demographic characteristics of study participants.

Variables	Cases N(%)	Control N(%)	Statistics	P
Sex				
Male	31(62.0)	32(64.0)	$\chi^2 = 0.043$	0.5000
Female				
Mean age (Year)	19(38.0)	18(36.0)	$t = 0.519$	0.605
Level of education Completed	36.44 \pm 8.22	35.40 \pm 11.53		
(Primary)	7(14.0)	2(4.0)		
Secondary	26(52.0)	32(64.0)	$\chi^2 = 3.420$	0.180
Tertiary	17(34.0)	16(32.0)		

Primary: At least 1–6 years of education.

Secondary: 7–12 years of education.

Tertiary: > 12 years of education.

$p \leq 0.05$: Significant.

χ^2 : Chi-square value.

t: Student *t*-test value.

Table 2
Frequency distribution of clinical/laboratory variables in patients with HIV infection.

Variable	N	%
1. PCV (%)		
20–29	25	(52.1)
≥ 30	23	(47.9)
2. CD ₄ cell count (cell/l)		
≤ 200	33	(66.0)
200–499	15	(30.0)
≥ 500	2	(4.0)
3. Presence of opportunistic infections		
PTB	12	(24.0)
Oral cand	3	(6.0)
PTB + oral cand	4	(8.0)
PTB = skin herpes	1	(2.0)
CNS toxoplasmosis	2	(4.0)
None	28	(56.0)
4. WHO Stage		
1	5	(10.2)
2	9	(18.4)
3	30	(61.2)
4	5	(10.2)
5. Weight (kg)		
30–39	5	(10.9)
40–49	12	(26.1)
50–59	21	(45.7)
60–69	6	(13.0)
≥ 70	2	(4.3)

N = Number of Patients.

Oral cand = Oral candidiasis.

Table 3
Study participants with severe neurocognitive impairment and minor neurocognitive disorder.

Participants	Cases	Controls	X ²	p
Participants with Total CSID Score below 2SD	11	0	12.350	≤ 0.001
Participants with Total CSID above 2SD	39	50		
Participants with Total CSID Score between 2SD and 1SD	23	18	4.655	0.03
Participants with Total CSID Score above 1SD	16	32		

SD = Standard Deviation.

Severe neurocognitive impairment = Participants with total CSID score less than 2SD of the mean of the control.

Minor neurocognitive disorder = Subject with total CSID score that were between two 2SD and 1SD of the control mean value.

x² – Chi square test value.

p – Level of significance.

p < 0.05 = Significant.

Table 4
Comparison of cognitive performances between patients with HIV infection and Controls using CSID.

Cognitive	Cases (N = 50)	Controls (N = 50)	p
Functions subtest	Mean ± SD	Mean ± SD	
Comprehension	7.59 ± 3.25	10.42 ± 3.97	≤ 0.001
Language	26.86 ± 4.85	32.40 ± 4.6	≤ 0.001
Orientation	11.42 ± 1.61	11.96 ± 0.20	0.020
Attention	7.60 ± 0.97	7.60 ± 0.20	≤ 0.001
Praxis	1.08 ± 0.57	1.66 ± 0.48	≤ 0.001
CSID Total	66.32 ± 9.01	76.34 ± 6.50	≤ 0.001

SD – Standard deviation.

p- ≤ 0.3 – small effect sizes.

≤ 0.5–0.7 medium effect sizes.

≤ 0.8 – large effect sizes.

scores and total CSID scores in the patients (p < 0.05). Among the OIs, central nervous system toxoplasmosis caused the worst cognitive deterioration (p < 0.05).

The relationship between the socio-demographic/clinical variables of the patients with HIV infection and their cognitive performances were shown in supplement 1–3.

3.1. Education

There was no influence of education on the cognitive performance of the patients with HIV infection (p > 0.05). The effect sizes of the analyses were small for language, orientation subtests and the total CSID scores ($\eta^2 = 0.01$ – 0.04). The effect sizes were medium for attention/concentration and praxis subtests ($\eta^2 = 0.07$).

3.2. Age

There was no association between age and cognitive functions among patients with HIV infection (p > 0.05). The effect sizes were small for all the cognitive domains in the analyses.

3.3. Sex

The female patients with HIV infection performed significantly better than the male patients on the domains of attention and concentration (p < 0.05). There was no significant effect of sex on the domains of language, orientation, praxis and total CSID score in the patients with HIV infection (p > 0.05). The effect sizes were small in these analyses.

3.4. Weight

The effect of weight on cognitive function in patients with HIV infections were evaluated by doing the analyses for male and female HIV patients separately. The median weights for the males and females patients with HIV infection were 54 kg and 45 kg respectively. There was no influence of weight on cognitive performances in male patients with HIV infection (p > 0.05). Also, the effect sizes were small in the analyses except in the attention/concentration domain where effect size was medium (d = 0.63). There was no influence of weight on performances across the cognitive domains of the CSID in female patients with HIV infection (p > 0.05). The effect sizes of these analysis were small except for the language domain where the effect size was medium (d = 0.75).

3.5. World Health Organization (WHO) stage

There were no significant differences in the cognitive performances of the patients with late stages HIV disease (WHO Stage III & IV) and early stages HIV disease (WHO Stage I & II), p > 0.05. The effect sizes were small for these analysis (d < 0.5).

3.6. Presence of opportunistic infections (OIs)

The HIV positive patients without OIs performed significantly better in the domains of Orientation and total CSID scores when compared to the patients with OIs (p < 0.05). The effect sizes were medium in the domains of Orientation and total CSID scores also (d = 0.58–0.59). The effect sizes were small for analyses on the other cognitive domains in these analysis.

3.7. Types of opportunistic infections (OI)

The patients with CNS Toxoplasmosis performed poorly on the domains of Language, Orientation, Attention/Concentration and Total CSID when compared to HIV patients with other OIs (p < 0.05). The

Table 5
Relationship between clinical variables and cognitive functions in patients with HIV infection.

Variables	N	Language		Orientation	Attention	Praxis	Total CSID
		Compr.	Expression	Mean	Mean	Mean	Mean
1. Presence of opportunistic infections							
Yes	22	4.86	25.50	10.91	7.45	1.05	63.32
No	28	5.00	27.93	11.82	7.71	1.11	68.68
p	0.13	0.08	0.04	0.35	0.71	0.04	
2. Types of Opportunistic Infections							
PTB	12	5.00	26.33	11.50	7.75	0.92	65.58
Oral cand.	3	5.00	25.33	12.00	8.00	1.33	68.67
PTD + Oral cand.	4	4.75	28.50	11.50	7.75	1.25	67.25
PTD + Herpes simplex	1	5.00	24.00	8.00	6.00	1.00	55.00
CNS Toxo.	2	4.00	15.50	6.00	5.00	1.00	38.00
p	0.60	0.02	≤ 0.01	≤ 0.01	0.80	≤ 0.01	

effect sizes were large in the analyses.

3.8. Anaemia

There was no influence of anaemia on the cognitive performances in patients with HIV infections in this study ($p > 0.05$). The effect sizes were small in the analyses.

3.9. CD4 cell count

There was no association between CD4 Cell Count and performance across cognitive domains of CSID in the patients with HIV in this study ($p > 0.05$). The effect sizes were also small for these analyses.

4. Discussion

Neurocognitive impairment (NCI) is an important complication of HIV infection worldwide and this ranged from asymptomatic neurocognitive impairment (ANI) to HIV – associated dementia (HAD). HIV-associated dementia is the most dreaded type of NCI that are observed in patients with HIV infection. The prevalence of NCI differed among studies due to different methodological approaches and choice of normative data utilized in those studies [20,21]. The prevalence of severe NCI among patients with HIV infections in developed countries such as USA in the pre-ART era was 47% [21]. The prevalence of NCI in patients with HIV infection in some African countries such as Cameroon, Botswana, Uganda and Central African Republic were 21%, 38%, 27% and 25% respectively [22–25]. In this study a prevalence rate of 22% was observed for severe NCI in patients with HIV. The reasons for the varying prevalence figures observed may be due to different neuropsychological instruments that were used in these different studies.

In this study using the CSID, the cognitive domains that were assessed were language, memory, attention/calculation and praxis. Previous Nigerian Studies showed that the patients with HIV were worse on neuropsychological functions in the domains of language, attention/concentration and the total CSID scores [18,19]. Another Nigerian Study by Imam et al. showed that the patients with HIV infection performed worse than controls on cognitive functions assessment using the Mini Mental State Examination scale [26]. In this study, similar observation were made as the patients with HIV infection performed poorly when compared to normal control subjects on the domain of language, orientation, attention/concentration and praxis.

Various factors have been observed previously to be associated with poor neurocognitive performances in patients with HIV infections and these included alcohol/substance abuse, cardiovascular/metabolic diseases, psychiatric disorders, hepatitis virus subtypes, anaemia, presence of opportunistic infections, CD4 Cell counts and so on [27]. In this study we were able to evaluate only the influence of gender, age, sex, level of education disease severity (WHO Stage, CD4 cell count) presence of

opportunistic infections on cognitive performance in patients with HIV infection.

The influence of gender on NCI is unclear as there were conflicting reports on this issue. Chiesi and AIDs in Europe Study group [28] reported that cognitive function were worse in women with HIV infection while another study reported more severe cognitive impairment in men with HIV infection [29]. In this present study, there was no influence of gender on cognitive performance (Language, Memory, and Praxis) in the patients with HIV infection and this is keeping with the findings from some previous studies [30–32]. The isolated findings of better performance of the female patients with HIV infection on Attention/Concentration in this study may need to be further explored.

The impact of age on neuropsychological performance have been documented in patients with HIV infection [23,25,29,30,34,35]. In some other studies, patients age was not associated with cognitive performance in patients with HIV infections [1,18]. The findings from this present study agreed with the latter studies. The reasons for the discrepancies on the influence of age or cognitive performance in patients with HIV infection might be due to differences in age limit used to categorize the patients and the different sample sizes of the various studies. Also majority of the patients in this study (69%) were in the middle age group.

It has been suggested that low level of education is an important determinant of poor cognitive performances in patients with HIV infection while some studies did not find any association between the level of education and cognitive performance in patients with HIV infection [1,31]. Our finding from this study is an agreement with the latter studies where the level of education did not influence patients performances in the domain of Language, Memory, Attention/Concentration & Praxis probably because the level of education has little influence on the performances on CSID which was the test instrument utilized in this study [25]. Also majority of the patients in this study (66%) were having less or equal to 12 years of education.

Weight loss have been associated with impaired neurocognitive functioning in the general population who were seronegative to HIV infection [36]. A study reported memory impairment and reduced verbal learning in patients with HIV infections [37]. A Brazilian study [31] found no association between the body mass index and performances of patients with HIV on cognitive assessment using NIMSE. In this study, no relationship was found between patients weight and their performances in the domains of Language, Orientation. Attention/Concentration and Praxis and this is in agreement with the later study.

An increases risk of NCI was found in patients with severe HIV disease (Late stages of HIV infection). Patients in WHO stages III & IV and CDC stage III were found to have severe NCI in some studies [4,38,39]. However, in this study, the clinical stage of HIV disease was not associated with cognitive performances in the patients and this was similar to the finding of a study in Bangui, Central African republic [25] where HIV infected patients with late stages HIV diseases did not differ

from those in early stages of HIV diseases on cognitive function testing. The HIV infected patients with low CD4 (< 200 cells/ μ L) count have been found to have NCI in several studies [19,22,38,40–43], while some other studies found no association between CD4 counts and neurocognitive performances [1,18,25,31]. These latter reports were in keeping with our findings where there was no difference in cognitive performances between HIV- infected patients with CD4 cells count greater or lower than 200 cells/ μ L. The reason for this finding might be due to the majority of the patients in this study had low CD4 cell count.

The presence of opportunistic infections (OIs) may exacerbate the production of cytokines such as tumor necrosis factor, Interleukin 6 which are toxic to the central nervous system neurons and this may lead to NCI in patients with AIDS defining illness. A study showed that it is only the combined effects of immune suppression and OIs that could lead to NCI [5,7,33,44]. In this study HIV-infected patients with OIs performed worse on the measures of orientation and total CSID scores when compared to those without OI. The reasons why the OIs have no adverse effect on the domains of language, attention/concentration and praxis in this study need to be explored in future larger studies. Two patients with central nervous system toxoplasmosis performed poorly on the measures of language, orientation, attention/concentration, praxis and total CSID scores when compared to the other HIV- infected patients with oral candidiasis pulmonary tuberculosis and skin herpes infection. This finding was in keeping with the report from Wang et al., where CNS toxoplasmosis and cryptococcal infections were strongly associated with HIV-associated dementia [45].

The presence of anaemia in a group of elderly people was associated with reduced activities of daily living [46]. In a Brazilian study [31] reduced haemoglobin concentration was also associated with poor cognitive performance on the MMSE scale. In this present study, presence of anaemia was not associated with cognitive functioning in the patients with HIV infection. The non-inclusion of patients with severe anaemia in this study might have accounted for this finding because patients with severe anaemia usually have low Karnofsky performance status and may not be able to conveniently undergo neuropsychological evaluation.

5. Conclusion

This study showed that patients with HIV infection presented late to the health facility for treatment and subsequently a high rate of NCI was observed.

5.1. Limitation

The study is limited by small sample size due to poor clinic attendance by patients with HIV infection and this may be due to high level of stigma that is associated with the illness in sub-Saharan Africa. Viral load assay were not done in the study because of cost and non- availability of this test in our center. Other causes of structural brain lesions or CNS infectious were not evaluated in these patients because of lack of resources for brain imaging and further laboratory testing in these patients. In this study, formal administration of Instrumental Activities of Daily living questionnaire were not done for the patients and future study should evaluate this in patients with HIV. The study is also limited by not comparing the patients to “gold standard” neuropsychological test batteries but our aim is to test the usefulness of a widely used, simple, readily available and inexpensive neuropsychological screening tool (CSID).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jensci.2017.10.001>.

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