HHS Public Access

Author manuscript

J Neurol Sci. Author manuscript; available in PMC 2016 June 14.

Published in final edited form as:

J Neurol Sci. 2009 October 15; 285(1-2): 149–153. doi:10.1016/j.jns.2009.06.043.

Risk factors for HIV-associated neurocognitive disorders (HAND) in sub-Saharan Africa: The case of Yaoundé-Cameroon

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Abstract

Background—The prevalence of HIV-associated neurocognitive disorders (HAND), especially HIV-associated dementia (HAD) is influenced by several risk factors. The prevalence as well as risk factors for HAD are not well known in sub-Saharan Africa (SSA). We have shown that the International HIV Dementia Scale (IHDS) is a useful screening tool for HAND in Yaoundé [Njamnshi AK, Djientcheu VdP, Fonsah JY, Yepnjio FN, Njamnshi DM, Muna WFT. The IHDS is a useful screening tool for HAD/Cognitive Impairment in HIV-infected adults in Yaoundé-Cameroon. Journal of Acquired Immune Deficiency Syndromes 2008;49(4):393–397], but no study in Cameroon has yet investigated the risk factors for HAND or HAD.

Patients and methods—Across-sectional study was conducted in Yaoundé, the capital of Cameroon from September to December 2006. One hundred and eighty-five HIV-positive subjects were included. Diagnosis of HAND was done using the IHDS with a score ≤ 10 considered as abnormal. Age, sex, level of education, IV drug use, body mass index (BMI), CDC clinical stage, CD4 counts, hemoglobin levels, administration of highly active antiretroviral therapy (HAART) and type of regimen used, were considered in univariate analysis, with level of significance set at $P \leq 0.05$. A binary logistic regression was used to determine independent risk factors.

Results—The following factors were independent predictors of HAND: advanced clinical stage (OR=7.43, $P=0.001$), low CD4 count especially CD4≤200/μL (OR=4.88, $P=0.045$) and low hemoglobin concentration (OR=1.16, $P=0.048$).

Conclusion—This first study of the risk factors for HAND in Yaoundé-Cameroon shows findings similar to those described in other studies. These results call for rapid action by policy makers to include HAND prevention strategies such as providing early universal access to HAART based on these risk factors, in the management of HIV patients at risk of HAND in resource-limited settings of SSA like ours.

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Author contribution: AKN and WFM designed the study. JYF and DMN recruited the patients and collected the data. AKN, ENT, AZL and JYF analyzed the data and wrote the paper. All authors made critical contributions to the paper and approved the final manuscript.

The authors have no conflict of interest to declare.

Keywords

HIV/AIDS; IHDS; Dementia; Risk factors; Cameroon; SSA

1. Introduction

In Cameroon, the national prevalence of HIV infection is 5.1% [1]. We have reported that possible HIV-associated dementia (HAD) or HIV-associated neurocognitive disorders (HAND) may be more frequent in Cameroon with a prevalence of 21.1% [2], than our earlier estimations [3,4]. This high prevalence represents a heavy disease burden for the country and would significantly compromise patient's quality of life. This may well be the case in most of the countries of sub-Saharan Africa (SSA). The treatment of HIV/AIDS and HAD with highly active antiretroviral therapy (HAART) has significantly modified the clinical course of HAD as several studies in different regions around the world have shown an improvement in cognitive and neuropsychological function in adults and children by HAART [5–14] independently of the type of HAART regimen. The identification of patients at risk of HAD in SSA may reduce its burden through an early institution of HAART, independently of classical criteria for HAART eligibility.

Several factors have been found to be associated with the risk of developing HAD. These include: low hemoglobin levels, low body mass index (BMI), more constitutional symptoms before AIDS, older age at AIDS onset, IV drug use, low CD4 counts, high plasma viral loads and antiretroviral (ARV) drug naivety [15–18]. However, studies that have examined these factors in resource-limited countries of SSA like Cameroon are rare.

We recognize that this study was done before the research nosology of neurocognitive disorders in HIV-infected subjects had been changed and we therefore use the terminology HAND to refer to the whole spectrum of the disorders (including HAD).

2. Methods

2.1. Study setting

The Day Care Unit of the Central Hospital of Yaoundé is the first of several HIV follow-up and treatment centers in the country, created by the Ministry of Public Health through the National AIDS Control Committee. It is a well recognized treatment center in which about 23,000 HIV-positive patients are followed-up, of whom 6000 are currently on antiretroviral therapy (HAART). The center receives a wide spectrum of patients from most parts of the country and eligibility criteria for HAART in Cameroon are: asymptomatic HIV-positive subjects with <200 CD4 cells/μL, or HIV-positive subjects with recurrent infections and <350 CD4 cells/μL or subjects with clinical CDC stage C disease.

2.2. Patients and data collection

One hundred and eighty-five HIV-positive patients recruited consecutively in the Day Care Unit, which is the HIV outpatient clinic of the Central Hospital of Yaoundé in the capital city of Cameroon from September to December 2006. These patients constitute a subset of

204 HIV-infected subjects we have reported earlier, studied in a case– control model for the usefulness of the International HIV Dementia Scale (IHDS) [2]. They were selected based on the availability of CD4 count results. The exclusion criteria were (1) current or past history of diffuse or focal Central Nervous System (CNS) disease; (2) head trauma; (3) current systemic disease; (4) alcohol abuse (CAGE questionnaire); (5) known psychiatric disease or treatment by antipsychotic drugs, and (6) body temperature of ≥37.5 °C at the time of recruitment. Those who accepted to participate in the study by signing an informed consent form were included irrespective of whether they were on HAART treatment or not.

The process of screening for HAND consisted of the administration of the IHDS as we have already described [2]. The score consists of four items including naming of four objects, finger tapping, the psycho-motor learning task, and a delayed recall of the four objects previously named. The IHDS was developed and evaluated in patient cohorts from Uganda (East Africa) and the United States [19]. Using a cutoff point of ≤10, this score had a sensitivity of 80% in the Uganda cohort. In our previous report on 204 HIV-positive patients and 204 controls, we have shown using the same cutoff point, that 21% of HIV-positive subjects had HAND while only 2.5% HIV-negative had an abnormal score (P=5.0×10^{-10}) [2].

In addition to screening for HAND, each patient underwent a complete medical history and physical examination including a thorough neurological assessment. Interviews were done in French, English or Pidgin English depending on the language best mastered by the subject. Additional information was obtained from the patients' case files. Handedness was determined using the BRYDEN index in situations of ambiguity [20]. Body weight was measured using a scale balance (Momert, Hungary) and read to the nearest 0.5 kg. The BMI was computed for each subject using subject height (measured with a standard stadiometer) and measured weight. Information on constitutional symptoms and signs including a past history of malaria was obtained, as well as IV drug use. Hemoglobin levels were determined alongside full blood counts using an automated Coulter counter. CD4 counts were done by automated machines through standard procedures and ARV treatment information was obtained from the patients and complemented and/or confirmed by the data in the case records. Due to limited resources, viral loads were not done. All data were recorded on questionnaires prepared for the purpose. Ethical clearance was obtained from the National Ethics Committee (NEC) and an administrative authorization for research was delivered for this study by the Minister of Public Health of Cameroon.

2.3. Data analysis

Data analysis was done using SPSS version 15.0 for Windows. The following data was included in the analysis: age, sex, marital status, level of education, profession, BMI, CD4 count, CDC Atlanta clinical stage, hemoglobin levels, and use of HAART. A hemoglobin cutoff point of 10 g/dL was used to define anemia. This cutoff point was used because it is easy to remember, and is midway between that of McArthur et al. (10.6 g/dL) and Brokering and Qaqish (9.5 g/dL) [17,21]. The CD4 count did not follow a normal distribution. We therefore transformed the distribution of the CD4 count by taking the square root of each value.

HAND or possible HAD was defined as the IHDS score ≤10 as in our previous report [2]. In the univariate analysis, continuous variables were recoded into categorical variables for the purpose of establishing trends across various categories of the variable. Pearson Chi Square test, Ficher's Exact Test, and the Student's *t*-test; were used as necessary to determine associations between HAND and variables in univariate analysis, with the level of significance set at $P \leq 0.05$. After an orienting univariate analysis, a binary logistic regression analysis was performed to determine the variables that remained significantly associated with HAND, after controlling for the variance of the other variables.

3. Results

3.1. General characteristics: (Tables 1a and 1b)

Out of the 185 participants in our study, there were 67% females and 33% males. The age range of the participants was 18–59 years, with a mean age of 37.6±8.8 years. The females were younger (mean age=36.2±8.6 years) than their male counterparts (mean age=40.3±8.6 years) (P=0.003). Most of the participants belonged to the 30–39 years (43%) and the 40–49 years (26%) respectively for both sexes. About 48% were married, 32% single, 14% widowed and 5% were divorced. Concerning the level of education, 52% had secondary education and 37% primary education while only 9% had higher education. The anthropometric measurements of our study participants (Table 1a) revealed that the mean BMI was 22.9±3.6 kg/m^2, with 7.6% of them having a BMI below 18.5 kg/m^2. The mean hemoglobin level was 11.1±2.3 g/dl with 31% having hemoglobin below 10 g/dl. About 52% and 13% of the participants were at the clinical stages B and C of the disease (CDC Atlanta Staging) respectively and 41% had CD4 counts below 200 cells/μL.

3.2. Prevalence and factors associated with HAD (Tables 2a and 2b)

Using the cutoff point for IHDS score of ≤10 to define HAND, we found that 22.2% of our study participants had a HAD. The presence of HAND was neither influenced by age, sex, marital status, level of education nor profession. In the univariate analysis, the mean hemoglobin (P=0.007) and the mean square root of CD4 count (P<0.001) were significantly lower in the HAND than non-HAND subjects. In addition, the risk of developing HAND was demonstrated to increase significantly with decreasing levels of CD4 count (P=0.009), advancing clinical stage of AIDS (P=0.001) and decreasing hemoglobin levels (P=0.008) but precisely hemoglobin levels ≤10 g/dL (P=0.006). The use of HAART (P=0.162) and weight loss (P=0.383) did not seem to be associated with HAND in a significant manner in the current study.

Controlling for the variance of each of variable significantly associated with the development of HAND in the univariate analysis with respect to the variance of the other variables in a binary logistic regression, CD4 count below 200 cells/μl, CDC clinical stage C and hemoglobin level ≤10 g/dL remained independently associated with development of HAD (Table 3).

4. Discussion

The aim of this study was to determine for the first time in Cameroon, the risk factors for possible HAND including dementia. One clinical and two biological variables emerged as independent predictors of HAND.

HAND occurred in all stages of HIV infection, but the risk increased with advanced infection. In fact, the prevalence of HAND more than quadrupled as one moved from clinical stage A to C (9.4% to 45.8%). More precisely, stage C disease was an independent predictor of HAND. The mean square root of CD4 count of the HAND group was significantly lower than that of the non-HAND group ($P<0.001$). Furthermore, the risk prevalence of HAND was over four times higher in participants with CD4 counts of 200 cells/μL or below (33.3%) than in participants with CD4 counts of 500 cells/μL and above (8.0%) ($P=0.009$). A CD4 count of 200 cells/μL or below stood out as an independent risk factor for HAND in logistic regression analysis. These findings are similar to results of other studies that have shown that the risk of having HAND is higher with lower CD4 counts and advanced disease [16–18]. Ours is the second risk factor study for HAND in SSA after the report by Wong et al. [18]; however, we have found a third independent risk factor, namely low hemoglobin level.

Several studies have suggested that HAART is essential in the management of HAD [5,9,12,22–27]. In our study sample, participants on HAART were less likely candidates for HAND (17.1%) than participants who were not on HAART (25.7%), although this difference was not statistically significant ($P=0.162$). This finding should nevertheless be interpreted with caution as the duration of HAART was not regularly reported in patients' records, making it difficult to evaluate the real effect of such treatment on HAND. Nevertheless, our data also lends some support to the conclusion of the second assessment of neuroAIDS in Africa conference in 2006, that HAART should be provided for HIV-positive patients in SSA with neurocognitive impairment (regardless of CD4 status) if confounding factors such as CNS opportunistic infections, delirium from an acute systemic process, or preexisting conditions have been ruled out as a cause for cognitive impairment [14]. The implication of our findings is that eligibility for HAART could be considered irrespective of CD4 count in patients at risk of HAD. Thus, by allowing the nearly 10% of patients in CDC stage A and those in stage B at risk of HAD to benefit from HAART, the treatment gap would be reduced, neurological complications would be reduced, resulting in a decreased incidence of HAD.

Although there is a difference in CSF penetration of antiretroviral drugs (with better rates of penetration observed with NNRTI, ZDV and protease inhibitors in that order), the type of HAART regimen with respect to CNS penetration no longer appears to be a determining factor from recent evidence [28, 29]. This has important implications for HAART policy in general for SSA.

Ford et al. have argued recently that if “the battle to start providing antiretroviral therapy in the developing world has been won, the battle to provide the best care we can is just beginning” since the policy of rationing Antiretroviral Therapy in Africa has led to an

unfortunate situation where we are treating too few, too late [30]. Furthermore, Brinkhof et al. have reported recently that mortality of HIV-infected patients treated with combination HAART in SSA continues to be higher than in the general population, but for some patients excess mortality is moderate and reaches that of the general population in the second year of HAART [31]. As commented in this paper, these findings support further expansion of strategies that increase access to HAART in SSA and suggest the excess mortality among HIV-infected patients in this region might be largely prevented by an early initiation of HAART, before an individual's HIV infection has progressed to advanced stages. Finally, Pitt et al. have just demonstrated evidence confirming the health-related quality of life benefits of HAART in a South African antiretroviral therapy program [32]. Some of these health-related benefits may have included prevention or improvement of HAD in the patients.

In our study, the mean hemoglobin level of patients with HAND was significantly lower than that of patients without HAD (P=0.007) in univariate analysis. Using a cutoff point of 10 g/dL, patients with anemia had a higher risk of HAD than those without (P=0.006). This cutoff point was used because it is easy to remember, and is midway between that of McArthur et al. (10.6 g/dl) and Brokering and Qaqish (9.5 g/dl). A similar study by McArthur et al. also found that low hemoglobin level was a co-factor for HAD [17]. Indeed, in our current study, hemoglobin was independent risk factor for the development of HAD with a relative hazard of 0.59 per additional 2 g/dL. Our data therefore lend further support for a systematic control and correction of anemia as part of the management of HIV-positive patients.

Age was not a determining factor for the prevalence of HAND in our study sample. This finding agrees with studies by Kissel et al. which showed that older seropositive individuals were not at an increased risk for HIV-related cognitive impairment when normal age-related cognitive changes were considered [33]. Our results also showed that sex was not a predisposing factor for the occurrence of HAND. This finding differs from that of Chiesi et al. as well as other studies which suggested an increase in the risk of developing HAD with increasing age [34] and a higher risk in women [16]. It should be observed that our sample was drawn from the cases in a case–control study design, where the cases were tightly matched for age and sex. This could be responsible for our observations concerning age and sex. Nevertheless an analysis of different age ranges in these cases did not reveal any significant association with these variables.

In our sample, BMI did not seem to influence the risk of developing HAND although those with BMI below 18.5 kg/m^2 were relatively at higher risk, but not so in a significant manner. Factors such as level of education, marital status and profession were not found to be associated with a risk of having HAD.

We recognize that this study was done before the research nosology of neurocognitive disorders in HIV-infected subjects had been changed [35] and we therefore use the terminology HAND in this paper to refer to the whole spectrum of the disorders (including HAD).

4.1. Study limitations

A noteworthy shortcoming of this study was the non-use of a full battery of neuropsychological tests to compare with and confirm the results of the IHDS screening test. That is why we have preferred the generic to use the term HAND. Nevertheless, the IHDS has been shown to have an acceptable level of sensitivity as a screening tool for HAD [19]. Furthermore, other possible predictors of HAD like the nadir CD4 count, the plasma and CSF viral load could not be determined systematically because of the non-prospective nature of the study design and limited resources. Brain imaging and CSF analysis could not be done due to logistical difficulties. However, possible confounding conditions were excluded as best as possible through careful history taking and clinical examination. None of the subjects had either a fever or a focal neurological sign to suggest a focal or diffuse CNS lesion.

5. Conclusion

The independent risk factors for HAND in Yaoundé-Cameroon are: advanced clinical stage, low CD4 counts especially CD4 ≤ 200/μL, and low hemoglobin concentration. These findings, reported for the first time in Cameroon—SSA, are similar to those described in other studies and call for rapid action by policy makers. These risk factors could be used to detect HIV-infected patients at risk of developing HAD, and included as criteria for eligibility to HAART. Universal access to HAART for these patients at risk of HAD, even in the absence of classical eligibility criteria for HAART, will reduce the risk of neurocognitive impairment and decrease the incidence of HAD in resource-limited settings of SSA like ours. Our current work is focused on confirming these results using a complete battery of neuropsychological tests, looking for molecular determinants of HAD and obtaining normative data in a healthy control group in Cameroon.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The write-up of this work was supported in part by the National Institutes of Health grant MH080611 (AKN and GDK). The authors acknowledge the collaboration of all the patients and subjects in this study. May they here find expressed our gratitude.

We also thank the team of the Day Care Unit and the Neurology Department team working under Prof. Njamnshi for collaborating in recruitment of study subjects.

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Table 1a

Characteristics of study sample: continuous variables.

Variable	No. of participants	Mean	Standard deviation	Minimum	Maximum
Age (years)	185	37.6	8.8	18.0	59.0
IHDS score	185	10.9	0.9	7.0	12.0
BMI (kg/m^2)	185	22.9	3.6	15.4	38.2
CD4 count (cell/μL)	185	264.5	194.2	1.0	1012.0
Hemoglobin (g/dL)	185	11.1	2.3	3.4	16.9

Table 1b

Characteristics of study sample: categorical variables.

Variable	Category	Frequency	Percent
Total	Total	185	100%
Age group	18–29	35	19%
	30–39	79	43%
	40–49	48	26%
	50–59	23	12%
Level of education	Higher education	16	9%
	None	3	2%
	Primary	69	37%
	Secondary	97	52%
Sex	Female	124	67%
	Male	61	33%
Marital status	Divorced	10	5%
	Married	89	48%
	Single	60	32%
	Widowed	26	14%
Profession	Agriculture	11	6%
	Business	31	17%
	Health worker	3	2%
	Housewife	38	21%
	Other profession	49	26%
	Student	4	2%
	Teacher	13	7%
	Unemployed	30	16%
	Military/Security officers	6	3%
	Total	185	100%
HIV dementia	Non-possible HAD/HAND	144	78%
	Possible HAD/HAND	41	22%
HAART	No	109	59%
	Yes	76	41%
Weight level	Over weight (BMI≥25 kg/m^2)	46	24.9%
	Normal weight (18.5≤BMI<25 kg/m^2)	125	67.6%
	Under weight (BMI<18.5 kg/m^2)	14	7.6%
CD4 count (cells/μL)	201–500	85	46%
	500+	25	14%
	Below 200	75	41%
Hemoglobin level	Level A (Hb≥11 g/dL)	90	48.6%
	Level B (8.0≤Hb≤10.9 g/dL)	77	41.6%
	Level C (6.0≤Hb≤7.9 g/dL)	14	7.6%
	Level D (Hb≤5.9 g/dL)	4	2.2%

Variable	Category	Frequency	Percent
Anemia Status	Anemia (Hb≤10 g/dL)	58	31%
	No anemia (Hb>10 g/dL)	127	69%
CDC Clinical stage	A	64	35%
	B	97	52%
	C	24	13%

Table 2a

Factors associated with possible HAD/HAND in univariate analysis.

Variable	Categories	*N*	HAD/HAND + ve, *n*(%)	HAD/HAND − ve, *n*(%)	*P*-value
Total	Total	185	41 (22.2%)	144 (77.8%)	
CD4 count	≤200	75	25 (33.3%)	50 (66.6%)	*P* = 0.009
	201–500	85	14 (16.5%)	71 (83.5%)	
	500+	25	2 (8.0%)	23 (92.0%)	
Hemoglobin level	Level A (Hb≥11 g/dL)	90	14 (15.6%)	75 (84.4%)	*P* = 0.008
	Level B (8.0≤Hb≤10.9 g/dL)	77	18 (23.4%)	59 (76.6%)	
	Level C (6.0≤Hb≤7.9 g/dL)	14	6 (42.9%)	8 (57.1%)	
	Level D (Hb≤5.9 g/dL)	4	3 (75.0%)	1 (25.0%)	
Anemia status	Anemia (Hb≤10 g/dL)	58	20 (34.5%)	38 (65.5%)	*P* = 0.006
	No anemia (Hb>10 g/dL)	127	21 (16.5%)	106 (83.5%)	
CDC clinical stage	A	64	6 (9.4%)	58 (90.6%)	*P* = 0.001
	B	97	24 (24.7%)	73 (75.3%)	
	C	24	11 (45.8%)	13 (54.2%)	
Weight level	0ver weight (BMI≥25 kg/m^2)	46	7 (15.2%)	39 (84.8%)	*P* = 0.383
	Normal weight (18.5≤BMI<25 kg/m^2)	125	30 (24.0%)	95 (76.0%)	
	Under weight (BMI<18.5 kg/m^2)	14	4 (28.6%)	10 (71.4%)	
HAART	Yes	76	13 (17.1%)	63 (82.9%)	*P* = 0.162
	No	109	28 (25.7%)	81 (74.3%)	

Table 2b

Factors associated with possible HAD/HAND.

Continuous variable	Possible HAD/HAND		Non-possible HAD/HAND		*P*-value
	Mean	SD	Mean	SD	
CD4 count (cell/μL)	173.20	160.77	290.53	195.52	0.001
Hemoglobin (g/dL)	10.19	2.74	11.31	2.15	0.007
BMI (kg/m^2)	22.28	3.65	23.09	3.61	0.212
Age (years)	36.90	7.48	37.74	9.17	0.591

Table 3

Independent risk factors of HAD/HAND (binary logistic regression analysis).

Risk factor for HAD/HAND	OR	95% CI		*P*-value
		Lower bound	Upper bound	
CD4 count <200	4.88	1.03	23.17	0.045
CDC clinical stage C	7.43	2.22	24.92	0.001
Hemoglobin ≤10 g/dL	1.16	1.00	1.31	0.048