

GENDER VARIATION IN THE RISK OF STROKE AMONG HIV- INFECTED PATIENTS
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ABSTRACT

Background: Recent Epidemiologic evidence suggested that Acquired Immunodeficiency Syndrome (AIDS) increases the chances of suffering from stroke, several literatures contained reports of thrombotic episodes occurring in patients with HIV infection; and various abnormalities predisposing to a hypercoagulable state have also been reported in such patients. Risk of stroke in non-HIV patients is higher in men than in women when considering individuals younger than age 80 years. However, few data exist to quantify the role of gender variation in the risk of stroke among HIV- infected stroke patients especially in the study area; the aim of this study was to find out if the baseline variables, including gender play a significant role in the risk of stroke among HIV- Infected stroke patients. **Method:** This was a Hospital based case-control study. Sixty-five (65) stroke patients aged 20-68 years and sixty-five (65) age and sex matched controls were enrolled. A structured questionnaire was administered. Neurological examination was performed and computed tomography scan of the Brain done. Blood samples were taken for HIV 1& 2 screening using DETERMINE kit ELISA method. Double ELISA confirmed positive results. CD4 count was determined by flow cytometry and serum chemistry was also carried out. **Results:** The risk of HIV infection among stroke cases was significantly higher than in control subjects 13 (20%) versus 3 (4.6%), respectively; (p-value <0.008). Odds ratio for HIV infection among stroke patients was 5.17. Statistical analyses of other variables showed that, female gender; young age and low CD₄ count were significantly associated with the risk of developing ischaemic stroke. **Conclusion:** Human Immunodeficiency virus infection is a significant risk factor for ischemic stroke in the adult population of Northeastern Nigeria and that, the female preponderance as well as, the low mean CD₄ count among HIV sero-positive stroke patients in this study reflect the demography of HIV in our Hospital. Therefore, considering HIV in the differential diagnosis of ischaemic stroke of unknown origin especially in young female adults is worthwhile in Northeastern Nigeria and that, further methodologically sound studies are needed to better define the epidemiology of AIDS-associated cerebrovascular disease in the Nigerian population

Keywords: Stroke, Gender, HIV, CD₄, Immunosuppressant

INTRODUCTION

Previous retrospective case-control studies in this centre¹ and other parts of the world have reported potential predictors of stroke in HIV-infected individuals compared with those without a history of stroke.^{2,3} This study expands on existing knowledge by comparing the incidence of stroke as a specific endpoint in patients with HIV infection to a control population of non-HIV infected individuals. We investigated whether HIV is independently associated with stroke, the relationship of HIV infection to traditional vascular risk factors, and potential stroke risk factors unique to female/male HIV-infected individuals. HIV/AIDS in Nigeria has assumed a generalized epidemic disproportion. There is no state that is presently excluded from the HIV pandemic, meaning that both urban and rural areas are equally affected. Additionally, the disproportionate increase of HIV prevalence in women as compared to men is increasingly being acknowledged. In a multicentre study in the United States⁴ it was found that, the association between HIV and ischaemic stroke is significant only in women and is most pronounced in younger age groups.⁴

METHOD

This was a hospital-based, case-control study. The study population consisted of two groups namely: Cases, who were HIV- infected stroke patients; presenting to the University of Maiduguri Teaching Hospital (UMTH), and controls; who were HIV negative stroke patients presenting to the same hospital.

Sixty-five consecutive cases of stroke and sixty-five controls matched for age and sex; were enrolled in this study. Criteria for inclusion into the study were; (a) age above sixteen years, (b) Computed tomographic scan evidence of stroke. Previously diagnosed HIV positive patients and patients with computed tomographic scan evidence of intracranial lesions other than stroke were excluded. A standard questionnaire was administered to

each study participant after obtaining an informed consent. Information including, age, sex, occupational status and level of education, were obtained. Others included cigarette smoking, alcohol consumption, current use of drugs such as cocaine and amphetamine, and use of oral contraceptives in women. Information about a prior physician diagnosis of medical conditions, such as hypertension, diabetes, sickle cell disease, renal failure, congestive cardiac failure, and cardiomyopathy were obtained.

All study participants were examined by the investigators, and records made of the subject's weight, height, pulse rate, pulse rhythm, blood pressure, cardiac status oral thrush and lymphadenopathy. Results of investigations were recorded which includes a brain CT scan, , fasting blood glucose, resting ECG and serum cholesterol level. Blood samples were taken for HIV 1& 2 screening using DETERMINE kit ELISA method. Double ELISA confirmed positive results. CD4 count was determined by flow cytometry.

Statistical analysis was done using SPSS version 11(SPSS Inc. Chicago, Ill, USA). Risk factors for stroke were tested for Odds ratio. Means of two groups were compared using student t-test while proportions were compared using chi-square with Yates correction where appropriate. Any p-value less than 0.05 was considered significant.

RESULTS

One hundred and thirty subjects were enrolled in this study, sixty five cases and sixty five controls. (Table 1)

Table 1: Sex and Age distribution among cases and controls

AGE GROUP	SEX(CASES)		CASES	SEX(CONTROLS)		CONTROLS
	M	F		M	F	
15-24	1	1	2	1	1	2
25-34	5	4	9	6	10	16
35-44	10	8	18	15	9	24
45-54	5	3	8	6	4	10
55-64	11	9	20	6	5	11
≥65	4	4	8	1	1	2
TOTAL	36	29	65	35	30	65

The highest stroke frequency (20/65; 30.8%) occurred in the age group 55-64 years, while the lowest frequency (2/65; 3.1%) was observed in the age group 15-24 years (Tab.2). The minimum age was 20 years and the maximum age was 68 years.

Table 2: Sex and Age distribution among cases

AGE GROUP	SEX(FREQUENCY)		TOTAL	PERCENTAGE
	M	F		
15-24	1	1	2	3.1%
25-34	5	4	9	13.8%
35-44	10	8	18	27.7%
45-54	5	3	8	12.3%
55-64	11	9	20	30.8%
≥65	4	4	8	12.3%
TOTAL	36	29	65	100%

Mean age of all cases was 47.22 years. However, mean age of male cases (47.42 years) was higher than that of females (46.97 years) (Tab.3). p-value >0.896, hence not significant. Thus, there was no statistical difference in mean ages of male and female stroke patients. Among the cases 36 (55.2%) were males and twenty nine 29 (44.8%) were females. (table 3).

Table 3: Sex and Mean age distribution among cases

Sex	Mean age in years	Frequency
Male	47.42	36 (55.4%)
Female	46.97	29 (44.6%)
P-value >0.896		

The mean age of stroke patients with HIV disease was 36.38 years and the mean age of stroke patients without HIV disease was 49.92 years. P-value of 0.001 hence highly significant. Thus, the observed difference in age of stroke patients with HIV infection and age of stroke patients without HIV infection was statistically significant. (table 4)

Table 4: HIV status and mean age distribution among cases

HIV Status	Mean age in years
HIV+ve	36.38 years
HIV-ve	49.92 years

P-value of 0.001

Among the thirteen HIV positive stroke patients 8(61.5%) were females and 5(38.5%) were males, with female: male ratio of 1.6:1. (table 5)

Table 5: Sex distribution among HIV+ stroke patients

Sex	HIV+ stroke patients
Male	5 (38.5%)
Female	8 (61.5%)

female: male ratio of 1.6:1.

Forty five (45; 69.2%) stroke patients were found to be male hypertensives. In comparison, three (3/63; 4.6%) female subjects were found to be hypertensive. P- value <0.000, hence highly significant. Thus, the observed difference in frequency of hypertension between males and females was statistically significant, suggesting that, hypertension is a risk factor for stroke among males than females. The Odds ratio was found to be 46.5 also suggesting a strong association between male gender and risk of hypertension and stroke. (table 6)

Table 6: Sex distribution among cases with hypertension

Blood Pressure	Males	Females	TOTAL
Hypertensive	45	3	48

P-value <0.000

Eleven out of sixty five cases (11/65; 16.9%) were found to be male diabetic while one (1/65; 1.5%) was found to be a female diabetic. P-value < 0.002 hence significant. Thus, diabetes was significantly associated with gender and risk of stroke. The odds ratio of 13.037 showed a strong association

Table 7: Sex distribution among cases with diabetes

Blood Sugar	Males	Females	TOTAL
	11	1	12

The mean CD₄ count of HIV positive stroke patient was 224.92 in comparison the mean CD₄ count of HIV negative patients was 690.67. (P-value <0.001).

Table 8: Mean CD4 count level among HIV+ stroke patients and HIV-ve stroke patients

HIV status	Mean CD ₄ count (cells/cm ³)
HIV+ve	224.92±89.37
HIV-ve	690.67±67.26

Nine female (9/13, 69%) HIV positive stroke patients have CD₄ <200 cells/μl while four males (4/13, 31%) have CD₄ >200cells/μl

Table 9: Sex distribution and mean CD4 count level among HIV+ stroke patients

HIV status	Mean CD ₄ count (cells/cm ³)
HIV+ve Males	224.92±89.37
HIV+ve Females	69.67±167.26

DISCUSSION The highest frequency of stroke observed in the 55-64 years age group was similar to the frequency earlier reported in this hospital,⁵ but the mean age of 47.2 years in this study was significantly lower than the 54 years earlier reported and 55.6 years reported in south-western Nigeria⁶; this may be due to increase in the incidence of stroke in young adults, partly accounted for by HIV infection. Additionally, although there was no statistically significant difference in the mean age of cases and controls, there was significant difference between mean age of stroke patients with HIV disease (36.38 years) and mean age of stroke patients without HIV disease (49.92 years) which indicate that cerebral infarction is common among HIV/AIDS patients' particularly young adults. Additionally, the young age of the subjects underscores the likely causal relationship between HIV and stroke since the patients described in this study were young, more importantly stroke aetiologies in this study were not confounded by illicit drug abuse or oral contraceptive use which were exclusion criteria in this study.

Frequency of HIV infection of 20% among stroke patients in this study is remarkably similar to the 18% found in one retrospective study among black Africans⁷ and 15% of all strokes in young HIV- infected black Africans in KwaZulu-Natal province of South Africa.⁸ But is significantly higher than 4% reported in Kinshasa, Zaire⁹ and 5.4% among Thai young adults.¹⁰

The female: male ratio of 1.6:1 among HIV positive stroke patients was close to 1.5:1 reported in black South Africans.⁷ This female preponderance may, therefore, be a reflection of the demography of HIV infection among black Africans.

In a recent comparative study from Boston health care system, between HIV cohort and matched non-HIV comparator cohort seen between 1996 and 2009; gender-specific analyses revealed a striking increase in ischaemic stroke risk in HIV-infected women compared with non-HIV-infected controls.⁴ It was also suggested that the increased relative

risk of ischaemic stroke in HIV-infected women may be explained by increased use of oral contraception or hormone replacement therapy among HIV-infected women; relatively greater differences in rates of traditional stroke risk factors including abdominal adiposity and inflammation,¹¹ differing efficacy of stroke prevention measures by gender,¹² Relatively increased stroke rates in HIV-infected women may also be explained by higher levels of immune activation compared with HIV-infected men after accounting for HIV RNA level.¹³

The female preponderance and low mean CD₄ count among HIV seropositive stroke patients in this study reflect the demography of HIV in our hospital in that, HIV in black Africans is chiefly acquired by heterosexual activity and females are more at risk of developing HIV infection than males. Findings of low CD₄+T-cell count among HIV infected stroke patients in this study is consistent with prior evidence that low CD₄+T-cell count may increase the risk of stroke in HIV-infected patients,^{14,15} is also similar to low CD₄ count found in (77%) black South African HIV positive stroke patients.¹⁶ Additionally, observational studies in other developing countries have suggested an association between immune dysfunction and stroke based on increased hospital admissions for young immunosuppressed HIV-positive patients with ischemic stroke in the absence of other obvious risk factors of ischemic stroke.^{17,18} This suggests the role of degree of immunosuppression as a determinant of development of neurological manifestation of HIV/AIDS.

Furthermore, The percentage of HIV-infected patients with traditional stroke risk factors including hypertension and diabetes mellitus was significantly higher than in the HIV negative cohort. (Figure 1)

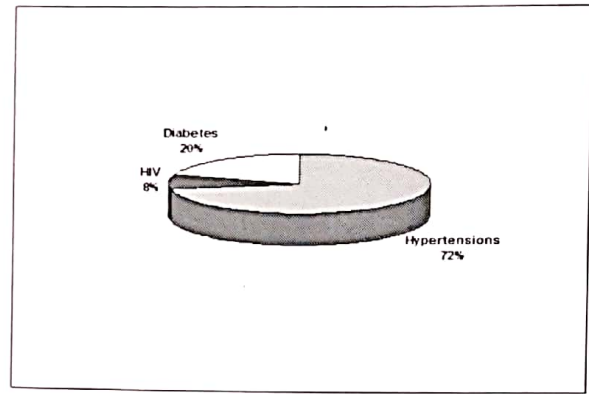


Figure 1: shows relationship between Hypertension, Diabetes and HIV among cases

CONCLUSION

Human Immunodeficiency virus infection is a significant risk factor for ischaemic stroke in the adult population of Northeastern Nigeria and that the female preponderance as well as, the low mean CD₄ count among HIV seropositive stroke patients in this study reflects the demography of HIV in our Hospital. Therefore, considering HIV in the differential diagnosis of ischemic stroke of unknown origin especially in young female adults is worthwhile in North eastern Nigeria and that, further methodologically sound studies are needed to better define the epidemiology of AIDS-associated cerebrovascular disease in the Nigerian population

LIMITATIONS

Firstly, the simultaneous determination of several variables in a relatively small sample size is one of the limitations of this study. Therefore, Careful interpretation is needed to differentiate the causality from traditional risk factors of stroke (which were more common in the HIV-infected individuals) and what may be an indication of HIV specific aetiology such as high viral load which was not assessed in this study. Additionally, sample size of 63 might have lacked power to detect difference with regards to risk factors like diabetes and hypertension, however, the sample size was increased to 65 in order to increase its sensitivity.

Secondly, this study was not able to address the issue of prothrombotic mechanisms. But several reports have already alluded to the frequency of anticardiolipin positivity and protein-S deficiency in patients with HIV related stroke which this study could not attempt to because of non-availability of reagents and manpower.

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