Ischemic stroke in young HIV-positive patients in Kwazulu-Natal, South Africa

Abstract—Cerebrovascular disease occurs in HIV-positive individuals, but no relationship between the two has been established. The authors reviewed a cohort of patients aged 15 to 44 years to evaluate stroke in HIV-positive and negative subjects. Patients who were HIV-positive with no other identifiable etiology were compared to age- and race-matched HIV-negative patients. HIV-positive and HIV-negative groups did not differ in angiographic, cardiac, or serologic tests. A positive HIV test does not provide causal information or diagnosis.

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Cerebrovascular disease occurs in HIV-positive individuals.^{1,2} Etiologies identified for stroke in HIV seropositive patients include meningitides due to cryptococcus, tuberculosis, neurosyphilis, and toxoplasmosis. Previous studies³ have included these patients when describing the HIV patient with a stroke. The neurology unit in Durban, KwaZulu-Natal (KZN), is the only unit that services a population of 8 million people. Most young patients with stroke diagnosed in KZN are referred to our unit. Further, KZN has the highest estimated incidence of HIV seropositivity in sub-Saharan Africa, currently reported at 36%.⁴ We sought to determine whether HIV seropositivity confers a predisposition to stroke by comparing age-matched HIV-positive and HIV-negative black African patients with cerebrovascular disease.

Methods. We reviewed charts of young patients with stroke (ages 15 to 44) admitted between 1987 and 2002. Characteristics recorded were demographic data such as age, sex, and race, and history of risk factors including hypertension, diabetes mellitus, smoking, alcohol abuse, elevated cholesterol levels, triglycerides, previous transient ischemic events, strokes, peripheral vascular disease, cardiac disease including myocardial infarction, and atrial fibrillation. Blood investigations included HIV status, erythrocyte sedimentation rate (ESR), anticardiolipin antibody (ACA), antinuclear factor (ANF), anti-neutrophil cytoplasmic antibody (ANCA), rapid plasma reagent (RPR), vitamin B12, antithrombin 3, and protein C and S levels. The findings on CT, MRI, cerebral angiogram, and echocardiogram were noted. The type of stroke (embolic or thrombotic), embolic source, and specific etiology, if known, were recorded.

Patients with venous sinus thrombosis, arteriovenous malformation, or intracerebral hemorrhage were excluded from the cerebral infarction group. Fisher's exact test was used for statistical analysis. The Wilcoxon rank sum test was used for serologic comparisons.

Results. We identified and reviewed 293 black African patients aged 15 to 44 years from a total of 594 patients with stroke. There was no major contribution from hypertension, diabetes mellitus, smoking, alcohol abuse, elevated cholesterol levels, elevated triglycerides, previous transient ischemic events, strokes, peripheral vascular disease, and cardiac disease including myocardial infarction and atrial fibrillation. This was assessed by comparing the frequency of these risk factors in the patients between the 15 to 44 age group and the rest of the stroke cohort. When comparing the over 44 age group with our young patient group, there was a difference for all the above risk factors between the groups ($p < 0.001$) except for atrial fibrillation ($p = 0.6$). This may relate to a predominance of young patients seen in our unit with unexplained strokes or rheumatic valvular heart disease. In the young stroke group there were 39 patients with hypertension (6 HIV+, 24 HIV-, 9 unknown [UK]), 6 with diabetes (1 HIV+, 5 HIV-), none with myocardial infarction, TIAs, peripheral vascular disease, or elevated triglycerides. There was one patient each with elevated total cholesterol and low-density lipoprotein cholesterol. There were 33 smokers (7 HIV+, 17 HIV-, 9 HIV-UK), and 23 drank alcohol (3 HIV+, 12 HIV-, and 8 HIV-UK). There was no history of binge drinking. There were five patients with atrial fibrillation (3 HIV- and 2 HIV-UK). There were 245 cerebral infarctions and 48 hemorrhages. There were 56 HIV-positive patients (51 with cerebral infarction and 5 with hemorrhage), 154 HIV-negative patients, and 83 in whom the HIV status was unknown. The mean ages (SD) for infarction were 31.3 (7.65) and for hemorrhage 33.5 (7.95) years ($p = 0.1$). In the HIV-positive group there were 29 female and 27 male patients. The HIV-negative group had 73 female and 81 male patients.

Ninety-eight of 158 (62%) angiograms were abnormal (table 1). No statistical differences were found for cardiac etiologies (table 2). Specific etiologies found in our patient cohort are shown in table 3. The etiologies have been further broken down according to HIV status. Serologic tests showed that the ESR values were higher in the HIV+ group ($p < 0.001$: Wilcoxon rank sum test); 4 HIV+ patients were also RPR positive (8.5%) as were 9 (7.14%) of the HIV- patients ($p = 0.7$: Fisher exact test); ACA positivity was detected in 1 (1.8%) HIV+ patient and 8 (5.2%) HIV- patients; and ANF was negative in all of the young black patients. The protein C and S were abnormal in only

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Table 1 Angiographic findings where angiograms were abnormal

No. (98)	HIV+	HIV-	Fisher exact test (p value)
ICA/CCA occlusion	34	7	0.2
MCA/ACA occlusion	16	12	0.7
VB occlusion	4	4	1.0
Vasculitis	12	9	0.7

1 of 16 patients tested. This patient was HIV-positive. The other 15 were young patients with arterial strokes in 13 and venous thromboses in 2. The 2 patients with venous thromboses were not included in the study. In these patients the HIV status was negative in 9 and unknown in 6. The OR for an ischemic stroke in HIV+ individuals was 2.3 (CI: 0.8 to 7.7) ($p = 0.09$ when comparing HIV+ patients with strokes with HIV- patients with strokes in the young group).

Discussion. Studies of the relationship between HIV and stroke have yielded conflicting results, partly due to small numbers of patients evaluated.^{2,3} In a study similar to ours,¹ no angiographic difference was found in 11 patients. A recent study of 15 patients with stroke included only 6 patients under age 44.⁵ Many of these had AIDS-defining illnesses and smoking as contributors to the stroke. A prospective small study⁶ of 35 hospital-based patients identified meningitis, cardioembolic sources, and protein S deficiency. Meningitis was excluded from our cohort, protein S was not routinely measured in many of our patients. The role of protein S deficiency in arterial strokes is unclear.⁷ Sickle cell disease is a rare disorder in South Africa but tests for this disorder should have been performed. CD4 counts were not routinely measured. However, as this study excluded AIDS-defining conditions, one may conclude that these patients were either early or in the stable period of their HIV infection. No patient was on antiretroviral therapy.

Studies limiting patients to infarction without AIDS-defining illnesses or alternate causes of cerebral dysfunction are few. We found no difference in cardiac disease or angiographic findings. However,

Table 2 Echocardiographic findings in HIV+ and HIV- patients

	HIV+	HIV-	HIV-UK	Fisher exact test (p value), HIV+ vs HIV-
Cardiomyopathy (n = 13)	1	6	6	0.6
Valvular heart disease (n = 19)	3	7	9	0.9
Infective endocarditis (n = 11)	1	4	6	0.9

HIV-UK = HIV status unknown.

Table 3 Specific etiologies found in young black patients with ischemic stroke (n = 245)

Diagnosis	No.	HIV+	HIV-	HIV-UK
Atheroma	3	0	3	0
Meningitis	9	3	6	0
Takayasu's arteritis	3	1	1	1
Moyamoya disease	3	0	2	1
Herpes zoster vasculitis	5	2	2	1
Cardiomyopathy	13	1	6	6
Rheumatic valvular heart disease	19	3	7	9
Infective endocarditis	11	1	4	6
Atrial fibrillation	5	0	3	2
Polycythemia	2	0	2	0
Fibromuscular dysplasia	2	0	2	0
Carotid artery dissection	1	1	0	0
No specific etiology found*	169 (68.9%)	39	89	41

* Does not refer to pathogenesis but specific etiology.

HIV-UK = HIV status unknown.

there was a trend toward more frequent ICA/CCA occlusions in the HIV+ group when compared to the HIV- group (see table 1).

Transesophageal echocardiography (TOE) was not routinely performed, but the yield from this test is low when the clinical examination, ECG, chest X-ray, and transthoracic echocardiogram are normal.⁸ Peculiar to HIV is an aneurysmal enlargement of large and medium sized extracranial and intracranial vasculopathy leading to infarction.⁹ The basis for this disorder is unclear but may be due to HIV itself.⁹ Postulates for infarction in HIV-positive patients without a specific cause include a prothrombotic state due to a rise in acute phase reactants, polyclonal gammopathy, and stimulation of cytokine networks. Population-based epidemiologic studies of cerebrovascular diseases have not been carried out in South Africa. Thus a denominator for examining the risk for stroke in HIV+ patients does not exist. This study showed an OR of 2.3, implying that the chances of having a stroke are greater if one is HIV+ than if one is HIV-. Although this was not significantly different from the HIV- group, there was a trend toward an increased risk. Similar relative risks were reported in a recent article.¹⁰ The traditional risk factors do not appear to apply to this young population group.

To date, this study has the largest HIV+ young stroke patient cohort that excludes the AIDS-associated etiologies. However, it needs to be validated with even larger numbers to increase its statistical power. Until then, a positive HIV test should not halt the search for alternate etiologies.

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NeuroImages

Figure. Cranial CT scan showing extended, bilateral basal ganglia calcifications, associated with minor calcifications at the border between the gray and white matter in the frontoparietal areas bilaterally and in the cerebellar gray matter.

VIDEO

Oculogyric dystonic states in early-onset parkinsonism with basal ganglia calcifications

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A 61-year-old woman with early-onset parkinsonism developed motor fluctuations with wearing-off and sustained dystonic oculo-

gyric states (DOS) 4 years after starting levodopa therapy (see supplementary video). All of the off-signs were exquisitely responsive to apomorphine. The benefit from each dose of levodopa lasted up to 2 hours; however, peak-dose dyskinesias appeared. Extraocular movements were normal in the on-phase. CT revealed marked intracranial calcifications (figure).

Oculogyric eye movements (OEM) in association with parkinsonism are pathognomonic of epidemic encephalitis lethargica.¹ Although postmortem analysis showed brain calcifications in some of these cases² DOS have not been reported in idiopathic basal ganglia calcification (Fahr syndrome). Similar to OEM occurring as levodopa-induced dyskinesias in Parkinson's disease DOS may be interpreted as a rare form of off-dystonia in long-term parkinsonism (figure).

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