Stroke in Black South African HIV-Positive Patients
A Prospective Analysis
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Background and Purpose—Stroke associated with HIV infection is poorly characterized. In this study we analyze the association in a black African population.

Methods—The clinical, laboratory, and radiological characteristics of 35 hospital-based black South African, heterosexual, HIV-infected patients who did not abuse intravenous drugs and presented with strokes were prospectively studied. The patients were antiretroviral therapy naive. Patients with other intracranial space-occupying lesions were excluded from the study.

Results—The age range was 20 to 61 years (mean, 32.1 years). There were 21 female and 14 male patients, with a female to male ratio of 1.5:1. Cerebral infarction occurred in 33 patients (94%) and intracerebral hemorrhage in 2 patients (6%). Underlying causes were identified in 30 of the 35 patients (86%) and included coagulopathies, meningitis, cardioembolism, and hypertension. The most common coagulopathy was protein S deficiency. No cause was found in 5 patients (14%).

Conclusions—The results are similar to data from studies on young black African stroke patients who are HIV negative. (Stroke. 2003;34:10-15.)

Key Words: blood coagulation disorders ■ HIV ■ stroke

Neurological involvement in patients with HIV infection occurs commonly. In 10% to 20% of HIV-infected patients, neurological symptoms are the first manifestation. Thirty percent to 40% of patients with AIDS develop clinical neurological dysfunction. At autopsy neurological involvement is present in up to 75% to 90% of cases with advanced AIDS.1,2

Symptomatic neurological disturbances include central nervous system (CNS) infections, CNS tumors, dementia, myelopathy, painful sensory neuropathy, and myopathy.1 CNS infections include cerebral toxoplasmosis, cryptococcosis, cytomegalovirus infection, and progressive multifocal leukoencephalopathy.1 Tumors that occur are primary CNS lymphomas and metastatic Kaposi’s sarcoma.1,2

Stroke as a manifestation of HIV infection is poorly characterized.1–3 This is primarily because most HIV/AIDS patients presenting with a clinical picture suggestive of stroke are more likely to have an underlying focal or diffuse CNS infection or tumor responsible for their symptoms.1,3

There have been several clinical and autopsy studies describing HIV-infected patients with stroke.3–24 In these studies vascular abnormalities, coagulation disorders, and cardioembolic disease were identified as the main cause(s) for the stroke.3–24 It is not known whether the HIV infection directly causes stroke.3–25

We describe here a prospective analysis of 35 adult black African HIV-infected patients with clinical and radiological stroke to determine the cause(s) in our patient population.

Subjects and Methods
The study design was a case series. We prospectively studied 35 adult (aged ≥18 years) HIV-infected patients presenting with stroke over a period of 20 months (November 1999 to June 2000). The patients were inpatients of the medical wards at the Chris Hani Baragwanath Hospital in Soweto, South Africa. The Chris Hani Baragwanath Hospital is a 3300-bed public university hospital that serves a predominantly black urban population of approximately 3 million people. All patients in the study were black, heterosexual, and did not abuse intravenous drugs. The patients were antiretroviral therapy naive.

Inclusion criteria were defined as presentation with any stroke and seropositivity for HIV-1 (diagnosed at presentation or earlier with patients’ informed consent). Stroke was defined in accordance with World Health Organization criteria as “rapidly developing clinical signs of focal, or at times global (as in coma or subarachnoid hemorrhage), disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than vascular origin.”26 The definitions of cerebral infarction and intracerebral hemorrhage (ICH) were based on the criteria of the National Institute of Neurological Disorders and Stroke.27 The presence of stroke had to be confirmed on CT scan. Patients with intracranial space-occupying lesion(s) other than stroke on CT scan were excluded from the study.
Clinical evaluation included a full risk factor analysis (hypertension, diabetes mellitus, smoking, history of cardiac disease or dyslipidemia, and use of hormonal contraceptives) and complete medical and neurological examinations.

Laboratory investigations included full blood count; erythrocyte sedimentation rate; C-reactive protein measurement; measurement of glucose, electrolytes, urea, and creatinine; liver function tests; CD4 counts; antinuclear factor tests; angiotensin-converting enzyme measurement; serological tests for syphilis, Toxoplasma gondii, and cysticercosis; polymerase chain reaction for herpes simplex, varicella zoster, and cytomegalovirus; and lipid profile. Coagulation studies included international normalized ratio, partial thromboplastin time, antithrombin 3, protein C, protein S, lupus anticoagulant, and anticardiolipin antibodies. In accordance with standard recommendations regarding clinical relevance of coagulation studies after an acute event such as a stroke, these were repeated on all patients at 3 months after presentation. Abnormalities of coagulation that persist are then interpreted as possibly causally relevant. Blood samples were also taken for assessment of cryoglobulins, cold agglutinins, and circulating immune complexes.

Cerebrospinal fluid (CSF) was analyzed for chemistry, cell counts, and cytology. Syphilis and toxoplasma serologies were determined. India ink staining and cryptococcal antigen testing were performed. Bacterial (including mycobacterial) and fungal cultures were obtained.

Radiological investigations included chest radiograph, brain CT scan, carotid Doppler studies, and aortic arch and 4-vessel cerebral digital subtraction angiography.

Cardiac evaluation comprised ECGs and transthoracic and transesophageal echocardiography.

Results
The patients’ main demographic and clinical characteristics, the presumed cause of stroke, and the relevant radiological, laboratory, and cardiac findings are reported in the Table and Figure. The total number of patients was 35.

Age and Sex
The age range was 20 to 61 years (mean, 32.1 years). There were 21 female patients and 14 male patients, with a female to male ratio of 1.5:1.

Clinical Presentation
Ten patients (28%) had isolated hemiparesis. Four patients (11%) presented with hemiparesis and hemisensory loss. Seven patients (20%) had hemiparesis with hemisensory impairment and hemianopia. Six patients (17%) had hemiparesis with hemisensory impairment, hemianopia, and aphasia. Three patients (9%) had hemiparesis with aphasia. Two patients (6%) had hemiparesis with aphasia and hemisensory loss. One patient (3%) had hemiparesis with aphasia and hemianopia. Isolated ataxia was the presenting clinical syndrome in 2 patients (6%). Stroke was the first manifestation of HIV infection in 20 patients (57%).

Radiology
CT scan revealed cerebral infarction in 33 patients (94%) and ICH in 2 patients (6%). In thirty-one patients the infarcts occurred in the anterior circulation; all were in the middle cerebral artery territory, with 19 being large vessel/cortical and 12 small vessel/subcortical. The remaining 2 patients had posterior circulation infarcts, both cerebellar. No hemorrhagic infarcts or venous strokes were noted.

Summary of Radiological and Cardiac Data

<table>
<thead>
<tr>
<th>Type of Examination</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan Infarct</td>
<td>33 (94)</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>31</td>
</tr>
<tr>
<td>Large vessel/cortical</td>
<td>19</td>
</tr>
<tr>
<td>Small vessel/cortical</td>
<td>12</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Angiogram Normal</td>
<td>15</td>
</tr>
<tr>
<td>Abnormal</td>
<td>7</td>
</tr>
<tr>
<td>Cut off</td>
<td>3</td>
</tr>
<tr>
<td>Vasculopathy</td>
<td>2</td>
</tr>
<tr>
<td>Atheroma</td>
<td>1</td>
</tr>
<tr>
<td>Carotid dissection</td>
<td>1</td>
</tr>
<tr>
<td>Cardiac evaluation</td>
<td>33</td>
</tr>
<tr>
<td>Normal</td>
<td>27</td>
</tr>
<tr>
<td>Abnormal</td>
<td>6</td>
</tr>
<tr>
<td>LVH</td>
<td>3</td>
</tr>
<tr>
<td>CM0</td>
<td>2</td>
</tr>
<tr>
<td>Mitral prolapse</td>
<td>1</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy; CM0, cardiomyopathy.

Carotid Doppler studies were done on all patients and showed no abnormalities. Cerebral angiography (digital subtraction angiography) was performed in a total of 22 patients and was normal in 15 patients and abnormal in 7 patients. The abnormal angiograms showed vessel cutoff in 3 cases (distal internal carotid artery in 2 and proximal middle cerebral artery in 1 patient), diffuse vasculopathy with multiple...
stenotic lesions involving small and medium-sized vessels in 2 cases, atheromatous plaque on the lateral wall of the carotid bifurcation with no significant stenosis in 1 case, and extracranial internal carotid artery dissection in 1 case.

Cardiac Evaluation
Thirty-three patients underwent full cardiological assessment. This assessment was normal in 27 patients and abnormal in 6 patients. Three patients had hypertensive heart disease with left ventricular hypertrophy, 2 patients had cardiomyopathies (1 postpartum and 1 HIV-associated), and 1 patient had a mitral valve prolapse. No intracardiac blood clots were detected. None of the patients had atrial fibrillation or rheumatic valvular heart disease. No patient was found to have a patent foramen ovale.

CD4 Counts
Patients’ CD4 counts were measured at the time of presentation with stroke. The Centers for Disease Control (CDC) 1993 revised classification system for HIV infection and AIDS was used, as follows: category 1: CD4+ T lymphocyte count of >500 cells/mm³; category 2: CD4+ T lymphocyte count of 200 to 499 cells/mm³; and category 3: CD4+ T lymphocyte count of <200 cells/mm³. Eight patients (23%) were classified as CDC category 1, 13 patients (37%) were classified as CDC category 2, and 14 patients (40%) were classified as CDC category 3.

CSF Analysis
Thirty-three patients had lumbar punctures. Lumbar punctures were contraindicated in 2 patients because of ICH with mass effect in one and a massive infarct with midline shift in the other patient. CSF studies were normal in 15 patients (45%) and abnormal in 18 patients (55%). Nine of the abnormal cases had meningitis (3 tuberculous, 1 pyogenic, 5 viral), 6 had an isolated raised protein, and 3 had isolated lymphocytosis. One of the latter cases was positive for varicella zoster on serology and polymerase chain reaction. None of the patients’ CSF was positive for herpes simplex, cytomegalovirus, syphilis, or Cryptococcus.

Blood Analysis
Stroke risk–related blood abnormalities were present in 20 of our patients (57%). Three of these patients had positive syphilis serology on specific and nonspecific testing. Five of these patients had anticardiolipin antibodies, 2 patients had circulating immune complexes, 11 patients had protein S deficiency, 1 patient had protein C deficiency, and 1 patient had disseminated intravascular coagulation with thrombocytopenia. None of the patients tested positive for Toxoplasma gondii, cytomegalovirus, or herpes simplex virus. In the remaining 15 patients (43%), no abnormalities were detected.

Nonneurological Illnesses
All patients were assessed for evidence of disease outside the nervous system. This was determined clinically (oral candida) or by radiological (chest x-ray) and blood investigations (syphilis, cisticercosis, toxoplasmosis, septicemia).

Twenty-five patients (71%) had concomitant nonneurological illnesses. Generalized lymphadenopathy was present in 13 patients. Six patients had oral candida. Three patients had pulmonary tuberculosis. Three patients had hypertension, and 2 patients had cardiomyopathy. One patient had herpes zoster ophthalmicus, 1 patient had Pneumocystis carinii pneumonia, and 1 patient had disseminated intravascular coagulation.

Ten patients (29%) had no nonneurological illness.

Presumed Etiologies
The strokes were grouped as either cerebral infarctions or cerebral hemorrhages. Of the 2 patients with ICHs, one patient with a lobar frontoparietal bleed had meningitis, and the other patient, a known hypertensive, had a typical hypertensive basal ganglia hemorrhage.

Thirty-three patients had cerebral infarction. In these patients >1 underlying cause was found in 10 patients. The causes in the cerebral infarct patients were as follows: 8 patients (25%) had meningitis (3 tuberculous, 1 pyogenic, and 4 viral); 3 patients (9%) had a potential cardioembolic source (HIV-related dilated cardiomyopathy, postpartum cardiomyopathy, and mitral valve prolapse); 2 patients had hypertension; and in 17 patients (49%) there was a coagulopathy. Of these latter patients, protein S deficiency occurred in 11 patients, protein C deficiency in 1 patient, and antiphospholipid antibody syndrome in 5 patients.

Vasculopathy/vasculitis occurred in 4 patients. One patient had a spontaneous extracranial internal carotid artery dissection resulting in a middle cerebral artery stroke, 2 patients had angiographically diagnosed vasculopathy (with small-vessel infarcts and normal CSF studies), and 1 patient had a herpes zoster vasculitis.

In 2 patients with large-vessel infarcts, markedly elevated levels of circulating immune complexes were detected. In the 10 patients with multiple possible etiologies, protein S deficiency co-occurred with tuberculous meningitis in 2 patients, with antiphospholipid syndrome in 2 patients, with viral meningitis in 1 patient, with herpes zoster vasculitis in 1 patient, with hypertension in 1 patient, and with protein C deficiency in 1 patient. The patient with pyogenic meningitis had co-occurrence of disseminated intravascular coagulation.

The patient with mitral valve prolapse had meningitis.

No potential cause was identified in 5 patients (14%).

Discussion
We have here documented the clinical, laboratory, and radiological features in 35 black South African heterosexual HIV-positive patients with stroke. We have not determined in this hospital-based study the epidemiological relationship between the occurrence of stroke and HIV in our population. The nature of this present study precludes any epidemiological observations because combined data, such as HIV sero-positivity and hospital admission statistics or stroke registers, are not available in our hospital setting. Several clinical, radiological, and postmortem studies have suggested a greater-than-chance association between HIV and stroke, but there remains controversy on this issue.2-25,30
In our HIV patients with stroke, the demographic data show that there was a slight female preponderance (female to male ratio = 1.5:1), with a mean age of 32.1 years. This reflects the demographics of HIV infection in our hospital. The HIV seroprevalence of adult admissions at our hospital in 1999 was 33% for female patients and 28% for male patients [A. Karstaedt, MBBCh(Wits), FCP(SA), unpublished data, 1999]. In the female patients there was 60% seropositivity in the group aged 25 to 34 years, and in male patients there was 37% seropositivity in this age group [A. Karstaedt, MBBCh (Wits), FCP(SA), unpublished data, 1999]. The female predominance and young age in our HIV-positive stroke patients thus merely relate to the demographics of the HIV/AIDS epidemic in our medical inpatient population.

In terms of the nature of the strokes, we found that 33 patients (94%) had cerebral infarcts and 2 patients (6%) had ICH. In most of the reported series, a much higher proportion of ICH was documented (32% to 39%).2–23 In these studies the common causes of ICH in the HIV-positive stroke patients were neoplastic and infectious intracerebral space-occupying lesions such as primary CNS lymphoma, metastatic Kaposi’s sarcoma, and cerebral toxoplasmosis.3 We excluded patients with intracerebral space-occupying lesions from our study.

In terms of the cerebral infarctions, we found a possible cause in 28 of the 33 patients, with coagulopathy being the most common. Seventeen of the 28 patients had a coagulopathy, and 11 of these patients had protein S deficiency.

Protein S deficiency has been associated with cerebral infarction in non–HIV-infected individuals.28,31,32 However, its role in predisposing HIV-infected patients to cerebral infarction is not well established.22,33–37 In HIV-infected patients, autoantibodies and the associated release of tumor necrosis factor-α have been shown to reduce protein S activity.38–41 How this correlates with the occurrence of stroke is not clear. A single retrospective case-control study showed a significant association of protein S deficiency in HIV-positive stroke patients compared with HIV-negative stroke patients.22 This concurs with our findings. However, we did not have HIV-negative stroke controls.

Elevated antiphospholipid IgG antibody titers were found in 5 patients with cerebral infarction. These autoantibodies are known to occur frequently in patients with HIV infection and AIDS.37,41–43 But the clinical relevance of this remains uncertain. The role of these antibodies in the pathogenesis of stroke in HIV/AIDS patients is not understood.3 Two of our patients had both antiphospholipid antibodies and protein S deficiency. This co-occurrence has been described previously in HIV patients but not in the setting of clinical stroke.41

Eight of our cerebral infarction patients had a stroke in the presence of an opportunistic meningeal infection. Cerebral infarction in association with meningitis is thought to be due to vasculitis.44

Isolated vasculopathy/vasculitis occurred in 4 of the patients with cerebral infarction. Of these, 1 patient had a spontaneous carotid dissection (unknown cause) with middle cerebral artery territory infarction, 2 patients had angiographically diagnosed vasculopathy (with small-vessel infarcts and normal CSF studies), and 1 patient had herpes zoster ophthalmicus. There is no clear evidence linking vasculopathy or vasculitis with HIV-associated stroke. Several clinical studies as well as a recent autopsy study concluded that in the absence of opportunistic CNS infections such as varicella, cytomegalovirus, tuberculosis, syphilis, Candida albicans, and tumors (CNS lymphoma), there is no evidence of cerebral vasculitis. In the autopsy study an HIV-associated vasculopathy was documented, which correlated only with pathological and not with clinical stroke.15

In 2 patients with large-vessel infarcts, markedly elevated levels of circulating immune complexes were detected. The presence of circulating immune complexes in HIV-infected patients is well recognized,45–47 but immune complex vasculopathy/coagulopathy associated with clinical cerebral infarction has not been described.

One patient with cerebral infarction had an HIV-associated dilated cardiomyopathy. This is well described in HIV infection.48 The cerebral infarction in this setting occurs on the basis of cardioembolism.

The cerebral infarction patients were further grouped regarding the affected vessels. The majority of patients had anterior circulation infarcts (94%). These were all localized to the middle cerebral artery territory. Of these, 61% were large-vessel infarcts with cortical involvement, and 39% were small-vessel infarcts with subcortical involvement. Similar findings have been noted in other series.24

A finding of interest in our study is that 20 of the 35 patients (57%) presented with stroke as the first manifestation of their HIV infection. There are only few case reports describing stroke as the presenting manifestation of HIV infection.49

With respect to the relationship between CD4 counts and the occurrence of stroke (cerebral infarction and ICH) in our patients, 77% had counts of <500 cells/mm³. This may reflect on the underlying etiologies as well as on the associated nonneurological illnesses in these patients. Twenty-five patients (71%) had concomitant nonneurological illnesses, the most common of which was generalized lymphadenopathy.

The patients described in this small study represent, to our knowledge, the largest series of prospectively collected and comprehensively characterized HIV-positive stroke patients. The patients in this series were young, and therefore the known risk factors for “stroke in the young” apply, and, not surprisingly, coagulopathies, vasculopathy, meningitis, cardioembolism, and hypertension were the most commonly identified causes. Importantly, our patients’ stroke etiologies were not confounded by intravenous or other illicit drug abuse. Smoking, oral contraceptive use, and dyslipidemia played no role as stroke risk factors. Our conclusions from this study are that in a black African HIV-positive stroke cohort, coagulopathies, meningitis, vasculopathies, cardioembolism, and hypertension will be identified.

For the results to be meaningful, one has to compare our data with data on young HIV-negative black African patients with stroke. We did not obtain this information in our population. However, there are several studies in black African patients that we can use for comparison. Some of these are directly relevant to southern Africa49–53; 2 refer to
black Nigerians\textsuperscript{54} and Kenyans.\textsuperscript{55} Two of these studies specifically investigated stroke in the young.\textsuperscript{53,55} The most common predisposing factors were found to be hypertension in 5% to 30%, cardioembolism in 8% to 22%, and meningitis in 5% to 15% of cases. This compares with hypertension in 9%, cardiac embolism in 9%, and meningitis in 26% in our series. Coagulopathies were not reported in these studies. In our series, as discussed above, protein S deficiency and antiphospholipid antibodies were found in 46% of patients, and 29% had multiple possible etiologies. Our findings thus concur with the literature on HIV-negative young stroke patients in terms of hypertension and cardiac embolism.

With respect to the high proportion of protein S deficiency and meningitis found in our study, a retrospective case-control study comparing stroke etiologies in young, predominantly African American subjects with and without HIV infection found meningitis in 25% and protein S deficiency in 20% of the HIV-positive cohort. This compares with meningitis in 26% and protein S deficiency in 31% of our patients. In this former study the authors concluded that meningitis and protein S deficiency were significantly associated with stroke in their HIV-positive patients.\textsuperscript{22} However, the relationship between the protein S deficiency and the occurrence of cerebral infarction was not clearly defined.\textsuperscript{22}

ICH occurred in only 6% of our patients but in 15% to 33% of cases in the comparable literature.\textsuperscript{49–55} In 5 patients (14%) no cause or risk factor for the stroke could be identified, which is similar to other series of young black African stroke patients (10% to 20%).\textsuperscript{53,55}

Our study has certain important limitations. First, the patients were hospital based, so that mild or minor strokes probably went undetected. Second, the study design and local limitations did not make it possible to obtain any epidemiological information or to draw any such conclusions. Third, there are no data available on the prevalence of protein S deficiency and antiphospholipid antibodies in our HIV-positive and HIV-negative populations.

Despite these limitations, we believe we can conclude that in a black African population with a high prevalence of HIV infection, a co-occurrence with stroke will be found. These patients will fall into the group of “young strokes.” Except for a higher occurrence of coagulopathies (mainly protein S deficiency) and meningitis and a lower occurrence of ICH, these patients have an etiologic and radiological profile similar to that of black African HIV-negative young stroke patients.

References


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