Stroke and HIV Infection

To the Editor:

We read with interest the report by Mochan et al regarding stroke in HIV-infected patients. This is an exceedingly relevant issue, given that both entities are common and the management of patients in whom both problems coincide is uncertain. The annual incidence rate of ischemic stroke in HIV was 216 per 100 000 in a large cohort, which is less than the stroke incidence of the whole population (>240 per 100 000 in the United States). However, stroke becomes more common in immunocompromised patients, particularly those with opportunistic central nervous system infections. Other important causes of stroke in HIV-infected patients are consequence of concomitant social issues rather than the effects of HIV itself, predominantly illicit drug use. Cocaine use, in particular, is a notorious factor associated with stroke in our community. Nevertheless, Mochan and colleagues did not include in their cohort patients with a history of intravenous or other illicit drug use. Other possible causes of stroke include infective endocarditis, meningovascular syphilis, injection injury to the carotid arteries, and secondary antiphospholipid antibody syndrome. In our view, physicians caring for HIV-infected individuals with stroke need to formulate 2 important questions: (1) Is a spinal tap indicated, and (2) does the patient have a coagulopathy?

Mochan et al reported a cohort of 33 patients with cerebral infarction and 2 with primary intracerebral hemorrhage. Almost all patients had a lumbar puncture and coagulopathy workup. Most patients were young, with mean age of 32 years. The authors assigned stroke etiology to 30 patients as follows, in descending order of frequency: “coagulopathies” (mostly protein S deficiency), meningitis, cardioembolism, and hypertension. These findings superficially appear to call for a systematic screening for coagulopathies and central nervous system infections in HIV-infected patients with ischemic stroke, although the authors restrained from specifically formulating such a recommendation.

Nevertheless, several criticisms can be raised from this article. Perhaps the most relevant is the absence of a critical distinction between HIV infection and AIDS. A diagnosis of AIDS is made in anyone with HIV infection and a CD4+ T cell count <200/mm3 or HIV-infected patients with infectious or neoplastic processes indicative of a severe cell-mediated immunodeficiency. Life-threatening complications of HIV infection, including meningitis resulting from opportunistic microorganisms, typically occur in patients with CD4+ T-cell counts <200/mm3. Although 14 patients had AIDS on the basis of a CD4+ T-cell count of <200/mm3, the authors did not specify whether the meningitis cases had lower CD4+ T-cell counts. This information appears crucial, given that stroke per se is not an indication for a spinal tap and about half of the reported patients did not have a previous diagnosis of HIV infection.

The interpretation of cerebrospinal fluid (CSF) results can be confusing in both ischemic stroke and HIV infection. Both conditions are associated with nonspecific elevation of CSF protein and lymphocytic pleocytosis. Unfortunately, the authors did not provide a detailed description of the CSF profile of their cases. The CSF was abnormal in 18 patients (55%); 9 had meningitis (3 tuberculous, 1 syphilitic, 5 viral), 6 had isolated protein elevation, and 3 had isolated lymphocytosis. However, it appears that most of the “viral” meningitis cases were not attributed to a specific pathogen; therefore, one could argue that these reflect HIV-encephalopathy.

Finally, attributing brain ischemia to protein S deficiency is somewhat naïve. Although abundant case reports and uncontrolled studies have encountered primary coagulation abnormalities in ischemic stroke, larger and better-designed studies have failed to corroborate such associations. Free protein S deficiency can be encountered in approximately 20% of patients with stroke, but it appears to be equally frequent in hospitalized control subjects. Something similar can be said about the antiphospholipid antibodies, which are common in several infections, including HIV patients, patients with acute vascular pathologies (deep vein thrombosis, stroke, myocardial infarction), and even normal people. The antibody titer and immunglobulin class are also relevant data (not provided by Mochan and colleagues), because the antiphospholipid antibody syndrome is associated with high and persistent titers of IgG and/or IgM.

We conclude that, to date, there is no compelling evidence to suggest that a spinal tap and/or thorough coagulopathy screening are necessary for every HIV-infected patient presenting with stroke. A spinal tap should be considered in patients with AIDS, those with signs and symptoms of meningitis, or those with questionable findings on neuroimaging. A coagulopathy screening, if deemed necessary, should be limited to the assessment of entities associated with arterial thrombosis such as antiphospholipid antibody syndrome and hyperhomocysteinemia. Like in any other patient with stroke, testing for protein S is an unnecessary recipe for confusion.

Lucas Restrepo, MD
Justin McArthur, MBBS, MPH
Department of Neurology
Johns Hopkins Hospital
Baltimore, Md


Response

The letter by Restrepo and McArthur discusses several issues relating to HIV and stroke. The article “Stroke in Black South African HIV-Positive Patients: A Prospective Analysis” described our experience at the Chris Hani Baragwanath Hospital, Soweto, Gauteng, South Africa. With regard to the criticisms directed at our article, we would like to address each of these as follows:

1. Illicit drug use, particularly cocaine, as a cause of stroke is an unknown entity in the black population in South Africa. We have no data on the extent of use and on any documented cases of drug-associated stroke in our patient population. We therefore excluded patients with any type of drug abuse. This separated the so-called social issues from HIV itself in relation to stroke.
2. A lumbar puncture was important in our study population because of the frequent occurrence of infections, particularly tuberculosis (TB). The incidence of TB in the Gauteng province was 315 of 100 000 population in 2001 (unpublished data obtained from Dr Riana Louw, Gauteng Department of Health, with permission). TB meningitis can present innocuously with no clinical signs of meningitis. In the analysis of patients with meningitis in our series, 3 patients were diagnosed with TB meningitis: 2 with CD4+ cell counts of <200 cells/mm3 and 1 with a CD4+ cell count of >200 cells/mm3. The patients with meningitis of presumed viral origin (HIV or other virus) had CD4+ counts of 200 cells/mm3. From a clinical point of view, we could not distinguish between these groups of patients. There were no overt signs of meningitis, and the only presenting finding was a sudden focal neurological deficit. If spinal taps were not performed on these patients, those with a diagnosis of TB meningitis would not have been identified.
3. Protein S deficiency and HIV-associated stroke have not been systematically studied. We reported our observation that coagulopathies, in particular protein S deficiency, occurred frequently in our patients. We agree that it is naïve to attribute brain ischemia to protein S deficiency. Antiphospholipid antibodies,
protein S deficiency, and other coagulopathies are common in infections, including in HIV-positive patients, patients with vascular events, and normal people.8,9 We have recently completed a study on and are submitting a paper on protein S deficiency in HIV-positive patients with stroke, HIV-positive patients without stroke, and HIV-negative patients with stroke. Our unpublished data indicate that protein S deficiency is not related to HIV-associated stroke.

In conclusion, we agree that a coagulation screen in HIV-positive patients with stroke should be limited to the assessment of “entities associated with arterial thrombosis.” However, we feel that the spinal tap is a necessary procedure in populations in which infectious diseases are frequent.

The management of HIV-associated neurological problems has to be tailored to the population being studied.8

Girish Modi, PhD, FCP, FRCP
Andre Mochan, FCP
Department of Neurosciences

Mala Modi, FCRad, MMed
Division of Radiation Sciences
School of Clinical Medicine
Faculty of Health Sciences

University of the Witwatersrand
Johannesburg, South Africa
