Stroke as the Initial Manifestation of the Human Immunodeficiency Virus

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Case Description
A 51-year-old man presented to the emergency department with acute onset of left-sided sensory loss and hemiparesis leading to a fall. The hemisensory loss had resolved at the time of presentation. He denied associated dysarthria, ataxia, visual field deficit, or aphasia. Furthermore, he had no current or history of headaches or seizures. The patient’s past medical history was significant for hypertension, anxiety, posttraumatic stress disorder and unilateral hearing loss after an explosion. Home medications included quetiapine, desvenlafaxine, amlopidine, benazepril/hydrochlorothiazide, and nebivolol, for which he was compliant. He did not smoke, drink alcohol, or use recreational drugs and was independent in activities of daily living. He denied unprotected sexual intercourse, intravenous drug abuse, and blood transfusions.

He presented 1 hour 29 minutes after last seen normal with a blood pressure of 163/97 mm Hg and was in normal sinus rhythm. Neurological examination revealed left hemiparesis with motor strength of 0/5 in left upper and 4/5 in left lower extremity; sensory deficits and cortical findings were absent. National Institutes of Health Stroke Scale score was 5. Given the acuity of focal symptoms, stroke was the leading diagnosis. An emergent head computed tomography did not show any acute intracranial pathology. Intravenous tissue-type plasminogen activator was administered and the patient subsequently admitted to the neurointensive care unit. Magnetic resonance imaging brain demonstrated acute right frontoparietal infarcts, with a distribution suggestive of a watershed infarct between the anterior and middle cerebral artery territories, and a second acute infarct in the left pons (Figure [A]).

A routine stroke workup was performed. Complete blood count and basic metabolic panel were normal. Urine toxicology was negative. Rapid plasma reagin was negative, and hemoglobin A1C was 5.5%. Lipid profile showed high-density lipoprotein of 19 (normal >39 mg/dL), but was otherwise normal. Computed tomographic angiography of head and neck showed no dissection, large-vessel occlusion, or high-grade extra- or intracranial stenosis. Transesophageal echocardiography demonstrated a left ventricular systolic function of 60% and was negative for valvular disease, intracardiac thrombus, left atrial dilation, and patent foramen ovale. Cardiac monitoring for atrial fibrillation was unremarkable. In light of the strokes involving different vascular territories and different vessel sizes, further workup ensued to evaluate for a hypercoagulable state and more intricate assessment of the intracranial vasculature with cerebral angiogram. The angiogram revealed multifocal areas of smoothly tapered narrowings involving the medium to smaller intracranial vessels consistent with nonatherosclerotic vasculopathy (Figure [B]).

Further workup was performed to rule out inflammatory or infectious conditions by blood and cerebrospinal fluid examinations. Screening for the human immunodeficiency virus (HIV) infection showed a positive ELISA; confirmatory Western blot subsequently established a new diagnosis of HIV. HIV viral load was 12,160 copies/mL (normal <40 copies/mL) and CD4+ cell count was reduced at 231 cells/mm³ (normal 535–1451 cells/mm³). In consultation with infectious disease, further testing was aimed at excluding opportunistic infection. A chest x-ray revealed no infiltrates, and quantiferon tuberculosis ELISA was negative. Cerebrospinal fluid appeared clear with 5 white blood cells, no red blood cells, normal glucose, and mildly elevated protein (52, normal 15–45 mg/dL). Cytology was negative for malignant cells; herpes simplex polymerase chain reaction and cryptococcal antigen were negative, as were serologies for mycoplasma pneumoniae, toxoplasmosis, and syphilis (VDRL [venereal disease research laboratory]) and polymerase chain reaction for varicella zoster virus. Cerebrospinal fluid bacterial and fungal cultures were also negative. From peripheral blood, inflammatory markers were elevated with sedimentation rate 82 mm/h and C-reactive protein 1.57 mg/L. Hepatitis screening and antineutrophil cytoplasmic antibodies and other vasculitides assays were negative. Hypercoagulability workup revealed mildly decreased Protein S (60; normal, 70%–150%), dilute Russell viper venom test (48; normal, <45), partial thromboplastin time lupus–anticoagulant (43;
normal, <40), β2 microglobulin (5.1; range, 0.8–2.2 mg/dL), and homocysteine (17.6; normal, 4.9–14.6 μmol/L). Protein C, lupus anticoagulant, and sickle cell testing were normal, and there were no mutations in the factor II or V genes. For secondary stroke prevention, aspirin and atorvastatin were started, antihypertensives were gradually resumed and highly active antiretroviral therapy (HAART) was begun.

Discussion

HIV infection is an independent predictor of ischemic stroke, particularly among women and younger age groups.1 With the advent of HAART and improved survival of HIV patients, the complications of chronic HIV infection, including stroke, are on the rise. Studies assessing stroke incidence have consistently shown a 1.4- to 1.5-fold increase of stroke in HIV-infected adults when matched to a non-HIV comparator cohort, with increased risk in patients with low CD4 cell counts and high HIV viral load.1,2 The number of stroke hospitalizations in the HIV population has risen by 60% from 1997 to 2006.2

The case presented in this report highlights the importance of HIV testing in younger patients with cryptogenic stroke. Based on clinical presentation (pure motor hemiparesis) and history of hypertension in this patient, we initially expected a multiple vascular territories and suggested involvement of blood vessels of different sizes. Laboratory evaluation revealed a new diagnosis of HIV infection and elevated inflammatory markers. Mild abnormalities were noted in the hypercoagulability evaluation, which may be related to the viral infection or recent stroke. The patient did not meet criteria for antiphospholipid syndrome, and no evidence was found for systemic vasculitis. Our patient also had a history of hypertension, a well-established risk factor for intracranial atherosclerosis. However, low-density lipoprotein was normal, and the angiographic findings were atypical for atherosclerotic changes. Atherosclerotic plaques are usually well defined, shorter rat bite lesions, preferentially affecting branching points of proximal vessels.3 These are frequently eccentric and have poststenotic dilatations. Our patient had smooth, tapered, segmental narrowings on conventional angiography, which is more typical for a nonatherosclerotic vasculopathy. HIV vasculopathy can mediate rapid progression of cerebrovascular stenosis, thereby causing recurrent strokes and is responsive to HAART therapy, which was initiated in our patient. However, without pathological examination, the definitive cause of the vasculopathy is uncertain, and we opted to also begin aspirin, statin, and antihypertensives for broad secondary stroke prevention.

The term HIV-associated vasculopathy is not well defined, but suggested to denote all indirect or direct vessel changes (both extra and intracranial) caused by HIV infection, after excluding secondary infectious or neoplastic cause.4 The pathophysiology of HIV-associated vasculopathy has not been well studied. Potential mechanisms for HIV-associated vasculopathy include aneurysm formation, vasculitis, endothelial dysfunction, accelerated atherosclerosis, as well as small-vessel disease changes and change in vasoreactivity, all of which play a role in mediating an increased risk for ischemic stroke.4 Besides vasculopathy, HIV infection can cause ischemic strokes through a multitude of other mechanisms, which include cardioembolism, opportunistic infections, neoplasm, coagulopathy, and hyperviscosity. Around 4% to 20% of ischemic strokes in HIV patients are caused by cardioembolism, predominantly caused by HIV-associated cardiomyopathy, pericardial disease, and endocarditis.5 Infection with HIV also predisposes patients to coagulopathies. Acquired protein S and C deficiencies, which present with recurrent venous thrombosis and rarely arterial thrombosis, has been found to occur at frequencies higher than the national average in HIV patients.6 Some opportunistic infections cause infectious vasculitis, most important of which are varicella zoster virus and cytomegalovirus. Varicella zoster virus has been shown to cause direct invasion of cerebral vessels and consequent inflammation and ischemia and should be excluded in all HIV patients, as targeted anti–varicella zoster virus therapy with acyclovir is effective.7

Figure. Neuroimaging confirms multifocal acute infarctions and intracranial vasculopathy. A, Magnetic resonance imaging brain demonstrates acute infarcts in right frontoparietal lobe with distribution suggestive of a watershed infarct involving the right middle and anterior cerebral arteries; and left pontine paramedian perforator infarct (top, diffusion-weighted imaging; bottom, apparent diffusion coefficient). B, Representative images of cerebral angiogram. Focal areas of smooth stenosis are present involving the right ACA (left) and left M1 segment (right). There is also involvement of right P1 segment. There is no significant extracranial vascular disease.
HAART therapy in itself has been known to cause metabolic syndrome and therefore predisposes to stroke and heart disease.8 HAART therapy containing nucleoside reverse transcriptase inhibitors, especially stavudine and some protease inhibitors are associated with increased prevalence of type 2 diabetes mellitus and glucose intolerance by inhibiting cellular glucose uptake and insulin resistance. Protease inhibitors and nucleoside reverse transcriptase inhibitors also cause elevated cholesterol, triglycerides, and dyslipidemia, which are also major risk factors for stroke. Protease inhibitors interfere with cytochrome P450 metabolism and regulation of thrombotic proteins, leading to a prothrombotic state with an abnormal coagulation profile with increased fibrinogen, D-dimer, and protein S deficiency, therefore pose an added risk of thrombotic events in HIV positive individuals.9 Therefore, besides advising on controlling modifiable vascular risk factors, like smoking, obesity, and hypertension, statins, and antithrombotic medications can be used in this population.

Stroke was the first manifestation of HIV infection in this patient who denied common HIV risk factors. The Center for Disease Control recommends routine screening for HIV infection even in asymptomatic individuals in all healthcare settings.10 However, recent data suggest that in patients with stroke, this is done only in a small number of patients, thereby missing a possible therapeutic window for early initiation of HAART and targeted secondary prevention of stroke. The utility of screening patients with stroke for HIV likely depends on the HIV prevalence in the region, but its recognition is critical for management. Treatment includes aggressive control of traditional vascular risk factors and initiation of HAART. Consultation with specialists in infectious diseases may assist in choosing antiretroviral medications with the lowest cardio- and cerebrovascular risk profiles. In the case presented, HIV testing in the screening for cryptogenic stroke not only helped identify the stroke cause but also established a diagnosis in an otherwise asymptomatic individual with the benefit of initiation of HAART.

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Disclosures
None.

References

TAKE-HOME POINTS
• HIV is a modifiable risk factor for ischemic stroke.
• Stroke may be the first manifestation of HIV.
• HIV testing should be a part of the stroke workup in cryptogenic stroke especially in the young.
• Highly active antiretroviral therapy therapy is integral to secondary stroke preventative measure in HIV patients.

Key Words: acquired immunodeficiency syndrome ■ enzyme-linked immunosorbent assay ■ HIV ■ mutation ■ stroke ■ vasculopathy
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