Increased Cortical Cerebral Blood Flow in Asymptomatic Human Immunodeficiency Virus-Infected Subjects

Souvik Sen, MD, MS, MPH,* Hongyu An, PhD,† Prema Menezes, PhD,‡ Jonathan Oakes, BA,‡ Joseph Eron, MD,‡ Weili Lin, PhD,§ Kevin Robertson, PhD,‖ and William Powers, MD‖

Background: Human immunodeficiency virus (HIV)-infected individuals are at high risk for ischemic stroke. To investigate the physiological basis for this risk, we used magnetic resonance imaging (MRI) to measure oxygen extraction fraction (OEF) and cerebral blood flow (CBF) in treatment-naive asymptomatic HIV-infected subjects and controls. *Methods:* In treatment-naive asymptomatic HIV-infected subjects and age-, gender-, and race-matched controls, OEF was measured by MRI asymmetric spin–echo echo-planar imaging sequences and CBF was measured by MRI pseudocontinuous arterial spin labeling. *Results:* Twenty-six treatment-naive HIV-infected subjects and 27 age-, gender-, race-matched controls participated. Whole-brain, gray matter (GM), and white matter OEF were not different between the groups (all $P > .70$). Unexpectedly, HIV-infected subjects had significantly higher CBF in cortical GM (72.9 ± 16.2 mL/100 g/min versus 63.9 ± 9.9 mL/100 g/min; $P = .01$) but not in subcortical GM ($P = .25$). *Conclusions:* The observed increase in cortical GM CBF in treatment-naive HIV-infected subjects is unexpected, contrary to CBF decreases reported in HIV-infected subjects on treatment, and may represent an initial increase in metabolic activity due to an HIV-mediated inflammation. **Key Words:** Cerebral blood flow measurement—cerebrovascular disease—MRI—infectious disease—inflammation.

Infection with the human immunodeficiency virus (HIV) confers an increased risk of ischemic stroke.[1-4] Stroke has often been reported as a complication of acquired immunodeficiency syndrome (AIDS); however, limited data exist that address the mechanism of the risk of HIV/AIDS-associated stroke. Epidemiological studies suggest that HIV-associated stroke affects a younger population with a risk factor profile that differs from the HIV-negative young stroke population in that hypertension, diabetes, hyperlipidemia, and smoking are not significant risk factors.[5] A limitation of many of the existing studies is that they fail to distinguish between strokes associated with medical conditions known to be associated with HIV infection, such as lymphoma, opportunistic infections, antiretroviral therapy, and substance abuse, and strokes resulting from an undetermined HIV-related process.[3,6] Several possible mechanisms have been hypothesized to account for stroke in association with AIDS, including a covert HIV-induced vasculopathy.[7,8] There is

From the *Department of Neurology, University of South Carolina, Columbia, South Carolina; †Mallinckrodt Institute of Radiology, Washington University in St. Louis, St. Louis, Missouri; ‡Division of Infectious Disease, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina; §Department of Radiology, University of North Carolina, Chapel Hill, North Carolina; and ‖Department of Neurology, University of North Carolina, Chapel Hill, North Carolina.

Received December 22, 2015; accepted March 22, 2016.

Funding for the study was provided by the National Institute of Neurological Disorders and Stroke R01NS062754.

Address correspondence to Souvik Sen, MD, MS, MPH, Department of Neurology, University of South Carolina School of Medicine, 8 Medical Park, Suite 420, Columbia, SC 29203. E-mail: Souvik.Sen@uscmed.sc.edu.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.03.045

also clinical and histopathological evidence suggesting that HIV infection may cause a variety of inflammatory vascular diseases.[9] Cerebral vasculitis during HIV infection and AIDS has been found in postmortem examinations.[10-12] Several case–control studies using single-photon emission computerized tomography (SPECT) have revealed baseline cerebral hypoperfusion. These studies have been reviewed by Tucker et al.[13] Recent magnetic resonance imaging (MRI) case–control studies have revealed cortical and subcortical gray matter (GM) hypoperfusion in asymptomatic HIV subjects.[14,15] Other studies have evaluated regional cerebral glucose metabolism using 18F-fluoro-deoxyglucose positron emission tomography (FDG PET) and noted a hypermetabolic state in the deep subcortical GM including the basal ganglia.[16-18] Although not demonstrated in the same patients, such a resting imbalance between blood flow and metabolism could produce a state the renders the brain more susceptible to minor degrees of subsequent ischemia. A similar imbalance between resting blood flow and oxygen metabolism leading to increased oxygen extraction fraction (OEF) is associated with a marked increased risk of stroke in patients with symptomatic carotid artery occlusion.[19] Only a single study has measured cerebral blood flow (CBF) and glucose metabolism with FDG in the same HIV-infected patients and, contrary to the previous studies, found no abnormality in either.[20] A recent MRI study on HIV subjects, most of them on antiretroviral therapy, found decreased CBF and a related uncoupling between CBF and cerebral oxygen metabolism ($CMRO_2$) changes during neuronal activation.[21] We used MRI to measure whole-brain and regional OEF and GM CBF in treatment-naive asymptomatic HIV-infected subjects and controls to gain insight into the pathophysiology of HIV/AIDS-related ischemic stroke.

Materials and Methods

Participants

Note that another arm of the present study included lowering blood pressure with an intravenous nicardipine infusion and all participants had to be able to safely participate in this part of the study.

HIV-infected patients were recruited through the Infectious Diseases Clinic at the University of North Carolina.

Inclusion criteria were as follows: (1) age 18 years or above, (2) recent detection of HIV infection without evidence of AIDS-defining illness, (3) being naive to antiretroviral therapy or within 7 days from the beginning of antiretroviral therapy, and (4) signed informed consent form.

Exclusion criteria were as follows: (1) use of antiretroviral drugs to treat HIV infection for more than a week or use of antiretroviral drugs in patients in whom antiretroviral therapy is not prescribed by the treating physician; (2) inability to cooperate with the performance of MRI; (3) radiological evidence of multiple hemispheric cerebral infarcts (larger than 1 cm in diameter) on prior MRI scan obtained for other reasons or screening MRI scan (scout film) obtained as part of the study MRI protocol, reviewed by the investigator; (4) mean arterial pressure less than 90 mmHg; (5) concurrent treatment with alpha-1 receptor blockers (doxazosin, terazosin, and prazosin) or hydralazine; (6) use of CYP3A4 inhibitors that may increase the levels/effects of nicardipine; example inhibitors include azole antifungals, ciprofloxacin, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, propofol, quinidine, and verapamil; (7) Pregnancy; (8) contraindications for MRI such as history or documentation of implanted ferromagnetic material or other devices (e.g., cardiac pacemaker) or claustrophobia; (9) history of aortic stenosis; (10) known allergy to nicardipine; (11) resting heart rate of 130 beats/min; (12) significant atrioventricular conduction abnormalities (second- or third-degree atrioventricular block); (13) known history of significant cardiovascular disease (history of congestive heart failure, myocardial ischemia, or cardiomyopathy) or peripheral vascular disease (symptoms of critical limb ischemia—ulcers or gangrene or ankle–brachial index less than .5; and (14) significant (≥70% by ultrasound) internal carotid artery stenosis/occlusion.

Healthy volunteers 18 years or above were recruited through institutional review board-approved local and newspaper advertisements and e-mail LISTSERV advertisements and flyers. Controls were matched on age (±2 years), gender, and race to cases and were tested for HIV infection. Control subjects met all of the above exclusion criteria.

Magnetic Resonance (MR) Measurements

MR measurements were acquired on a 3-T whole-body MR scanner (Trio; Siemens Healthcare, Erlangen, Germany) at the Biomedical Research Imaging Center at the University of North Carolina, Chapel Hill.

CBF

MR CBF images were acquired with a pseudocontinuous arterial spin labeling (pCASL). pCASL[22,23] employs a train of short RF pulses for pseudocontinuous labeling. Label and control images were acquired alternatively with a single-shot gradient–echo acquisition. The total labeling and control pulse durations were 2 seconds. A postlabeling delay time of 1000 milliseconds between the labeling or control pulses and the image acquisition was utilized. The labeling plane was placed 80 mm inferior to the imaging center. The field of view was 220 mm^2 and the matrix size was 64×64. Sixteen slices with a slice thickness of 5 mm without interslice gap were acquired. repetition time/echo time (TE) = 4000/11 milliseconds. Forty pairs of label and control images were acquired. The total data acquisition time was 5 minutes and 20 seconds. The labeling