HHS Public Access

Author manuscript

J Stroke Cerebrovasc Dis. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

J Stroke Cerebrovasc Dis. 2016 August ; 25(8): 1891–1895. doi:10.1016/j.jstrokecerebrovasdis.2016.03.045.

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

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Abstract

Background and Purpose—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 naïve asymptomatic HIV-infected subjects and controls.

Methods—In treatment naïve asymptomatic HIV-infected subjects and age-gender-race matched controls, OEF was measured by MRI asymmetric spin-echo echo-planar imaging (EPI) sequences and CBF was measured by MRI pseudocontinuous arterial spin labeling (pCASL).

Results—Twenty-six treatment naïve HIV-infected subjects and 27 age-gender-race matched controls participated. Whole brain, gray matter and white matter OEF were not different between the groups (all $p > 0.70$). Unexpectedly, HIV infected subjects had significantly higher CBF in cortical gray matter (72.9 ± 16.2 ml/100g/min vs. 63.9 ± 9.9 ml/100g/min; $p=0.01$) but not in subcortical gray matter ($p=0.25$).

Conclusions—The observed increase in cortical gray matter CBF in treatment naïve 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.

Keywords

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

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Disclosure: The authors have reported no conflicts of interest.

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, 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 vasculopathies.[7, 8] There is 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 MRI case-control studies have revealed cortical and subcortical gray matter hypoperfusion in asymptomatic HIV subjects.[14, 15]Other studies have evaluated regional cerebral glucose metabolism using FDG PET and noted a hypermetabolic state in the deep subcortical gray matter 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 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 CMRO2 changes during neuronal activation.[21] We used MRI to measure whole brain and regional OEF and gray matter CBF in treatment naïve 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 this 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: 1. Age 18 years or above. 2. Recently detected HIV infection without evidence of AIDS-defining illness 3. Antiretroviral therapy naïve or ≤ 7 days from beginning antiretroviral therapy. 4. Signed informed consent form

Exclusion criteria: Started on antiretroviral drugs to treat HIV infection more than a week or those in whom per the treating physician antiretroviral therapy is not indicated. 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 study MRI protocol, reviewed by the investigator. 4. Mean arterial pressure < 90 mm Hg 5.Concurrent treatment with alpha-1 receptor blockers (doxazosin, terazosin, prazosin) or hydralazine. 6. 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 130 beats/minute 12. Significant atrioventricular (AV) conduction abnormalities (2nd or 3rd degree AV 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 I < 0.5 14. Significant (≥70% by ultrasound) internal carotid artery stenosis/occlusion

Healthy volunteers 18 years or above were recruited through IRB approved local and newspaper advertisements and email listserv advertisements and flyers. Controls were matched on age (+/− 2 years), gender and race to cases and tested for HIV infection. Control subjects met all above exclusion criteria.

Magnetic Resonance Measurements

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

Cerebral Blood Flow—MR CBF images were acquired with a pseudo-continuous arterial spin labeling (pCASL). pCASL[22,23] employs a train of short RF pulses for pseudo-continuous 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 post labeling delay time of 1000 ms between the labeling or control pulses and the image acquisition was utilized. The labeling plane was placed 80 mm inferior to the imaging center. FOV was 220 mm^2 and matrix size is 64×64. Sixteen slices with a slice thickness of 5 mm without interslice gap was acquired. TR/TE= 4000/11 msec. Forty pairs of label and control images were acquired. The total data acquisition time was 5 minutes and 20 seconds. The labeling and control images were averaged separately and a low pass Gaussian filter with a full-width-half maximum (HWHM) of 11.4 mm (about 3.3 pixels) was utilized to improve signal to noise ratio (SNR). Quantitative CBF maps were calculated similar to a published method.[24] In addition to perfusion imaging, each session included a high resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) imaging with voxel size of 1×1×1 mm3 for anatomical reference for subsequent image registration and normalization.

Oxygen Extraction Fraction—Deoxyhemoglobin (dHB), an endogenous magnetic susceptibility source, causes mesoscopic magnetic field variations.[25, 26] The relaxation rate $R2'$ is proportional to the product of the concentration of dHb and the venous cerebral blood volume (vCBV). Regional cerebral venous oxygen saturation (SvO2) or OEF (SaO2-SvO2) can be measured if both $R2'$ and vCBV can be acquired. In this study, an asymmetric spin echo (ASE) single shot echo planar imaging (EPI) sequence was utilized.[27] An ASE EPI sequence is a variation of a single shot SE EPI sequence allowing variable time intervals between the $\pi/2$ and π pulses. The TE is the echo time, where τ is the time interval between the π pulse and TE/2. By varying τ while keeping TE constant, susceptibility-induced magnetic field changes can be evaluated. Details of this method can be found in previous publications.[27–29]

Data Analysis

The International Consortium for Brain Mapping (ICBM, McConnell Brain Imaging Centre, Montreal, Canada) brain template was utilized as an atlas to define several regions-of-interest (ROIs). A nonlinear symmetric diffeomorphic registration algorithm was utilized for aligning atlas T1 to each individual patient's T1 images (ANTS, PICSL, Philadelphia, PA, USA).[30, 31] A six-parameter rigid image registration was performed to align pCASL, ASE, and T1 images from the same subjects across all scans using FSL 3.2 (FMRIB, Oxford, UK). T1 images of each individual subject were segmented into white matter (WM), gray matter (GM), and CSF using the Markov Random Field-based tissue segmentation approach provided in FSL 3.2.[32] Regions of interest (ROIs) were manually defined to cover all acquired slices in both hemispheres. For each subject, the GM and WM masks were generated from T1 segmentation. Possible subject movement was corrected by Analysis of Functional NeuroImage software. Each region was manually delineated on high-resolution images. Quantitative CBF and OEF measurements were compared between the groups using unpaired t-test.

This study was approved by the local Institutional Review Board, and all subjects provided written informed consent before participating.

RESULTS

A total of 53 subjects consented to the protocol between the years 2010–2013: 26 were treatment naïve HIV-infected subjects (Mean age ± SD=29±7, 92% male, 35% white, 46% black and 19% others) and 27 were age-gender-race matched HIV-negative controls (Mean age± SD= 31±9, 93% male, 37% white, 53% black and 10% others). At the time of diagnosis the HIV-infected subjects had a mean CD4± SD =465±155 and mean $\log_{10}$ viral copies ± SD =4.2 ± 0.9 detected in blood and were studied within 2 weeks of diagnoses.

Whole brain, gray matter and white matter OEF were not different between the groups (all $p > 0.70$). (Table 1). Unexpectedly, HIV-infected subjects had significantly higher CBF in cortical gray matter (72.9 ± 16.2 ml/100g/min vs. 63.9 ± 9.9 ml/100g/min; p=0.01) but not in subcortical gray matter (64.5±14.4 ml/100g/min vs. 60.4±10.8 ml/100g/min; p=0.25).

DISCUSSION

In this study, we did not find an increase in OEF to explain the elevated stroke risk in HIV-infected patients. Unexpectedly, we did measure a statistically significant increase in cortical gray matter CBF in treatment naïve HIV-infected subjects compared to HIV negative matched controls, with no corresponding changes in the OEF.

We used a post-labelling delay of 1000 msec second for pCASL CBF measurements. This is shorter than the recently recommended minimum of 1.8 seconds.[33] A 1000 msec post-labeling delay does not produce accurate CBF measurement in white matter (and therefore for whole brain as well) because of the longer arterial transit time for white matter. Therefore, we are only reporting gray matter CBF. With a post-labeling delay of 1000 msec, underestimation of CBF will occur in gray matter regions with longer transit times.[34] However, since cerebrovascular disease produces longer transit times, this technical matter cannot explain the higher blood flow in the HIV-infected patients.

Our finding of increased cortical CBF is contradictory to several PET, SPECT and MRI studies that demonstrated global and regional cerebral hypoperfusion in asymptomatic HIV subjects. A PET and ASL-MRI study in HIV infected subjects on antiretroviral therapy noted an age dependent decrease in cerebral blood flow in the cortical gray regions, and an increase in cerebral blood flow in the subcortical white matter and gray matter regions, compared to the HIV negative controls.[20] Additionally, a recent MRI ASL study investigating the role of rCBF measurement as a preclinical biomarker of HIV induced brain injury, also found a significant decrease in rCBF in the lenticular nuclei and visual cortex in 33 HIV positive individuals, in comparison with 26 HIV negative controls.[15] Similar findings have been reported in SPECT and PET studies.[13] In these studies, the HIV infected subjects included a mix of early infected subjects and chronically infected subjects on antiretroviral therapy, and relatively older (mean age 39±2 years) compared with our patient population, possibly explaining the discrepancy with our CBF findings. A recent fMRI study has demonstrated an age dependent decrease in cerebral blood flow in HIV positive subjects, compared with HIV negative controls.[35] In addition, most of these studies that were conducted in the post-antiretroviral therapy era included subjects on antiretroviral therapy. The specific effect of antiretroviral therapy on cerebral blood flow and oxygen metabolism remains unknown.

Increased cerebral blood flow is seen in the early stages of brain inflammation caused by acute encephalitis, gradually decreasing to below normal levels in the subacute to chronic phases.[36, 37] A SPECT study performed on HIV infected subjects, prior to the advent of newer antiretroviral therapy in treatment of HIV, showed an initial increase in CBF followed by a time related decrease in uptake compared to normal controls.[38] The findings were attributed to an HIV mediated inflammatory reaction with increased blood flow and possibly activated macrophages and cytokine production.[38] This hypothesis of HIV mediated inflammatory response is further corroborated by a recent proton MR spectroscopy (^{1}H-MRS) study of asymptomatic HIV positive subjects naïve to antiretroviral therapy.[39] This study revealed findings of increased inflammatory brain metabolite markers Cho/Cr and MI/Cr that suggesting inflammation during early untreated HIV. Antiretroviral therapy

initiation during the first year of infection attenuated the increase of these inflammatory cerebral markers, but it did not appear to reverse them within the follow-up period.

Several prior FDG PET studies have reported increased glucose metabolism in the subcortical and basal ganglia region in HIV positive subjects.[13, 16–18] We did not directly measure cerebral oxygen metabolism ($CMRO_2$) in this study. However, according to the equation $CMRO_2 = CBF \times OEF \times CaO_2$, an increase in cortical gray matter CBF with no change in OEF would produce an increase in $CMRO_2$ unless there is a reciprocal decrease in the arterial oxygen content (CaO_2). We are currently performing additional studies with measurements of CaO_2 to address this issue.

In summary, we report increased cortical gray matter CBF, with no change in OEF, in newly diagnosed, treatment-naïve HIV-infected patients, suggesting an increase in metabolic activity due to an HIV mediated inflammatory reaction early in the course of the disease. Further studies in progress entail systematic collection of CaO_2 measurements for calculation of CMRO2 as well as repeat measure of CBF, OEF and CMRO after 12 months of antiretroviral therapy, providing an unique opportunity to measure the effects of treatments on these parameters.

Acknowledgments

Funding for the study was provided by: NINDS R01NS062754

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Table 1

Whole brain and regional oxygen extraction fraction and gray matter cerebral blood flow in HIV-infected subjects (N=26) and HIV negative controls (N=27).

	OEF	CBF
Whole brain		
HIV positive cases	0.40±0.04	
HIV negative controls	0.40±0.04	
t-test	0.78	
Cortical gray matter		
HIV positive cases	0.40±0.06	73.2±14.2
HIV negative controls	0.40±0.05	64.4±10.9
t-test	0.74	0.01
White matter		
HIV positive cases	0.40±0.03	
HIV negative controls	0.40±0.04	
t-test	0.94	
Deep gray matter		
HIV positive cases	0.40±0.04	64.5±14.4
HIV negative controls	0.40±0.04	60.4±10.8
t-test	0.87	0.25

OEF, oxygen extraction fraction; CBF, cerebral blood flow (ml per 100 g/min);

Values are mean±standard deviation