Cerebral Vasoreactivity is Impaired in Virally Suppressed HIV-infected Individuals

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Introduction

Rates of several vascular outcomes, including stroke, are higher in HIV-infected individuals than in age-matched uninfected controls.[1-5] Endothelial dysfunction and accelerated atherosclerosis related to HIV-associated chronic inflammation and immune activation may contribute to increased cardiovascular risk in this unique patient population.[6] The mechanisms underlying increased cerebrovascular risk in HIV infection, however, have not been investigated.

Cerebral vasoreactivity (VR), a measure of cerebrovascular endothelial function,[7,8] is associated with small vessel and severe large artery cerebrovascular injury.[9-13] One method to assess cerebral VR is measuring the vasodilatory response, or increase in mean flow velocity of the cerebral arteries, to inhaled carbon dioxide (CO_2).

The primary goal of the UNderstanding Cerebral VasoReactivity in HIV infection (UNCoVeR) study was to compare cerebral VR between treated, virally suppressed HIV-infected individuals and uninfected controls and to evaluate the effect of HIV-specific factors on cerebral VR.

Methods

Cross-sectional study of 65 HIV-infected adults and 28 uninfected controls recruited from SCOPE (Study of the Consequences of the Protease Inhibitor Era).

All HIV-infected participants were on a stable antiretroviral therapy (ART) regimen with undetectable plasma HIV RNA (<40 copies/mL) for a minimum of 24 weeks prior to the study.

Cerebral VR was assessed with the transcranial Doppler (TCD) CO_2 challenge. Cerebral VR was defined as the percentage change in mean flow velocity of the middle cerebral arteries per unit change in end-tidal CO_2 in response to a gas mixture of 6% CO_2 and 94% O_2. The decrease in mean flow velocity in response to hyperventilation was also measured as a secondary outcome.

Data on vascular risk factors, substance use and HIV-specific factors were collected from participants, the SCOPE database and electronic medical records when available.

We used mixed effects multivariate linear regression models adjusted for age, race and clinically relevant variables chosen by forward stepwise regression to determine the association between HIV and cerebral VR and between HIV-specific factors and cerebral VR.

Results

Table 1. Demographic and clinical characteristics.

	HIV-infected (n=65)	Uninfected (n=28)	P value
Demographics (% of total unless noted)			
Age (years), mean (SD)	57.2 (8.5)	53.5 (10.0)	0.071
Male sex	95	96	0.80
Non-white race/ethnicity	26	32	0.56
Vascular and other risk factors (% of total unless noted)			
Hypertension	49	29	0.065
Dyslipidemia	57	21	**0.002**
Diabetes mellitus	12	0	**0.052**
Coronary heart disease	5	0	0.25
Statin use	48	11	**0.001**
Aspirin use	49	21	**0.012**
Hepatitis C infection	23	4	**0.022**
Current substance use (% total unless noted)			
Alcohol use (yes/no)	55	79	**0.034**
<1 drink per day Up to 1 drink per day Up to 2 drinks per day Up to 3 drinks per day	45 40 9 6	21 61 11 7	**0.025**
Tobacco use (yes/no)	14	25	0.19
Cocaine use (yes/no)	5	7	0.62
Methamphetamine use (yes/no)	6	4	0.61
Marijuana use (yes/no)	48	21	**0.018**
HIV-specific factors			
CD4 count (cells/mm^3), mean (SD)	596 (251)	---	---
Nadir CD4 count (cells/mm^3), mean (SD)	242 (175)	---	---
Duration of HIV infection (years), mean (SD)	20.2 (6.8)	---	---
% with ART regimen containing: PI	42	---	---
Any NRTI	98	---	---
Abacavir	32	---	---
Any NNRTI	55	---	---
Integrase inhibitor	34	---	---
Maraviroc	5	---	---

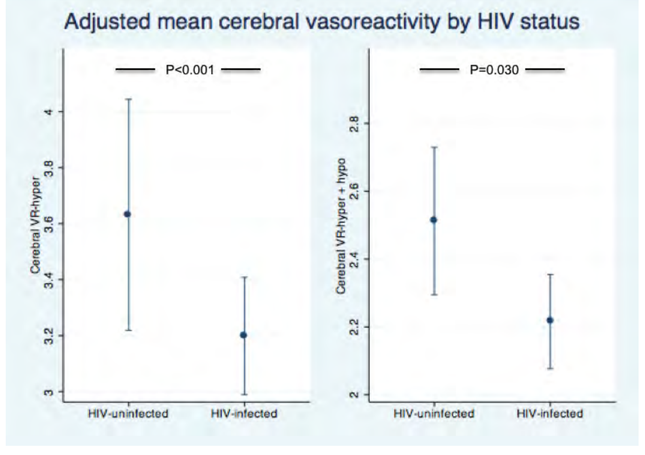
Table 3: Multivariate model of the effect of risk factors on cerebral vasoreactivity among HIV-infected cohort only. We did not find a statistically significant effect of most recent or nadir CD4 count, duration of HIV infection or ART class on cerebral VR among HIV-infected participants.

	HIV-infected only (n=65) Total observations (left + right sides) n=122	
	Difference in mean cerebral vasoreactivity (95% CI)	P value
Age (per 10-year increase)	-0.01 (-0.27 to +0.25)	0.95
Race (non-white versus white)	-0.80 (-1.32 to -0.28)	**0.003**
Diabetes mellitus	-0.84 (-1.54 to -0.14)	**0.018**
Statin use	+0.51 (+0.04 to +0.97)	**0.034**
Alcohol use (for each additional drink per day)	+0.27 (-0.005 to +0.54)	**0.054**
Tobacco use (current versus no current use)	-0.47 (-1.14 to +0.20)	0.17
Methamphetamine use (current versus no current use)	-0.90 (-1.83 to +0.04)	0.060

Table 2. Multivariate model of the effect of HIV infection and other risk factors on cerebral vasoreactivity. HIV infection was independently associated with lower cerebral VR, as were diabetes, non-white race and methamphetamine use. Statin use among HIV-infected participants was associated with higher cerebral VR, while it had no statistically significant effect on uninfected participants.

	HIV-infected (n=65) + Uninfected (n=28), Total observations (left + right sides) n=175	
	Difference in mean cerebral vasoreactivity (95% CI)	P value
HIV infection (in non-statin user)	-0.86 (-1.30 to -0.42)	**<0.001**
Age (per 10-year increase)	-0.08 (-0.29 to +0.13)	0.45
Race (non-white versus white)	-0.68 (-1.09 to -0.27)	**0.001**
Hypertension	-0.01 (-0.39 to +0.38)	0.97
Diabetes mellitus	-0.91 (-1.60 to -0.23)	**0.009**
Statin use for HIV-infected Statin use for HIV-uninfected	+0.51 (+0.06 to +0.96) -0.65 (-1.73 to +0.42)	**0.028** 0.24
Aspirin use	+0.39 (-0.03 to +0.81)	0.067
Alcohol use (for each additional drink per day)	+0.26 (+0.03 to +0.48)	**0.027**
Methamphetamine use (current versus no current use)	-1.13 (-1.90 to -0.36)	**0.004**

Figure 1. Adjusted mean cerebral VR by HIV status. Models adjusted for age, race, diabetes mellitus, hypertension, statin use, aspirin use, alcohol consumption, and methamphetamine use. Cerebral VR was evaluated using two outcomes: cerebral VR-hyper, which is the percentage change in mean flow velocity per unit change in end-tidal CO_2 in response to inhaled CO_2 , and cerebral VR-hyper + hypo, which is the percentage change in mean flow velocity per unit change in end-tidal CO_2 in response to inhaled CO_2 and hyperventilation. HIV infection was independently associated with lower cerebral VR using both outcomes.



Conclusions

Treated and virally suppressed HIV infection is an independent risk factor for reduced cerebral VR, a marker of clinical and subclinical cerebrovascular dysfunction.

Impaired cerebrovascular endothelial function may represent one potential mechanism to explain increased stroke risk in HIV-infected individuals.

Diabetes mellitus was strongly associated with lower cerebral VR, as was non-white race, while statin use was consistently associated with higher cerebral VR among HIV-infected individuals.

We did not find a statistically significant effect of most recent or nadir CD4 count, duration of HIV infection or ART class on cerebral VR in HIV-infected individuals.

Future studies should compare longitudinal changes in cerebral VR between HIV-infected and uninfected individuals and investigate the contribution of immune activation and inflammation to cerebrovascular dysfunction in HIV infection.

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