Title

Intracranial vascular imaging detects arterial wall abnormalities in persons with treated HIV infection

Journal

AIDS, 36(1)

ISSN

0269-9370

Authors

Chow, Felicia C

Callen, Andrew

Arechiga, Victor

et al.

Publication Date

2022

DOI

10.1097/qad.0000000000003064

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

AIDS. 2022 January 01; 36(1): 69–73. doi:10.1097/QAD.0000000000003064.

Intracranial vascular imaging detects arterial wall abnormalities in persons with treated HIV infection

Felicia C. CHOW, MD, MAS[1,2], **Andrew CALLEN, MD**[3], **Victor ARECHIGA, BA**[1], **David SALONER, PhD**[4], **Jared NARVID, MD**[4], **Priscilla Y. HSUE, MD**[5]

[1]Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, San Francisco, USA;

[2]Department of Medicine (Infectious Diseases), University of California, San Francisco, San Francisco, USA;

[3]Department of Radiology, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA;

[4]Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, USA;

[5]Department of Medicine (Cardiology); University of California, San Francisco, San Francisco, USA

Abstract

Objective: Although a substantial proportion of ischemic strokes in persons with HIV infection (PWH) is related to large artery disease, studies evaluating elevated cerebrovascular risk in PWH have focused primarily on microvascular disease. We compared the burden of intracranial large artery disease on vessel wall magnetic resonance imaging (VW-MRI) in PWH and HIV-uninfected individuals.

Design: Cross-sectional study

Methods: We recruited antiretroviral therapy-treated PWH with undetectable plasma viral load and HIV-uninfected individuals. All participants were ≥40 years of age and at moderate to high cardiovascular risk. We used Poisson and mixed effects logistic regression models to compare the number and associated characteristics of enhancing intracranial arteries on VW-MRI by HIV status.

Results: Of 46 participants (mean age 59 years), 33 were PWH. PWH had nearly four-fold as many enhancing intracranial arteries on VW-MRI than HIV-uninfected individuals (rate ratio 3.94, 95% CI 1.57–9.88, p=0.003). The majority of wall enhancement was eccentric (76%) and short-segment (93%), suggestive of intracranial atherosclerotic disease (ICAD). Sixty-nine

Address correspondence and request for reprints to: Felicia C. Chow, 1001 Potrero Avenue, San Francisco, USA, 94110; 628-206-4449, felicia.chow@ucsf.edu.

Author contributions: Design and conceptualization of the study (FCC, DS, JN, PYH), analysis and interpretation of the data (FCC, AC, VA, DS, JN, PYH), drafting the manuscript (FCC), and revising the manuscript (FCC, AC, VA, DS, JN, PYH).

CONFLICTS OF INTEREST

The authors report no conflicts of interest. Dr. Hsue reports honoraria from Merck and Gilead unrelated to this study.

percent of enhancing arteries were not associated with luminal narrowing on magnetic resonance angiography. None of these characteristics differed significantly by HIV status.

Conclusion: In persons at moderate to high cardiovascular risk, HIV infection, even when well-controlled, may be associated with a greater burden of intracranial large artery disease and, specifically, of ICAD. Studies of the mechanisms underlying higher rates of ischemic stroke in PWH should include evaluation for intracranial large artery disease. VW-MRI provides added value as an adjunct to traditional luminal imaging when evaluating cerebrovascular risk in PWH.

Keywords

HIV infection; stroke; cerebrovascular disease; intracranial large artery disease; vessel wall MRI; MRA

INTRODUCTION

Persons with HIV infection (PWH) are at higher risk of ischemic stroke compared with age-matched HIV-uninfected individuals.[1] Studies investigating the distribution of ischemic stroke subtypes in PWH have found that up to 40% of strokes may be related to large artery disease.[2] Moreover, large artery disease may be a more common stroke etiology in PWH than in HIV-uninfected individuals.[3] Despite these findings, cerebral small vessel disease has been the primary focus of neuroimaging studies evaluating cerebrovascular risk in PWH,[4] in part due to the association between small vessel disease and HIV-associated cognitive impairment.[5] In contrast, the contribution of intracranial large artery disease to HIV-associated stroke remains poorly defined. Understanding the role that large artery disease plays in HIV-associated stroke is critical, as intracranial atherosclerotic disease (ICAD) is considered to be the most common vascular lesion in stroke patients worldwide.[6]

Vessel wall-magnetic resonance imaging (VW-MRI) is an emerging technique that allows for high-resolution visualization of the vessel wall where arterial pathology originates. VW-MRI complements traditional vessel imaging techniques [e.g., computed tomography angiography (CTA), magnetic resonance angiography (MRA)], which may miss non-stenotic intracranial atherosclerotic lesions.[7] In addition, when combined with luminal imaging, VW-MRI may facilitate differentiation of ICAD from other causes of intracranial arterial disease based on enhancement characteristics.[8]

We compared the burden of intracranial arterial wall enhancement and associated characteristics on VW-MRI and time-of-flight (TOF) MRA between PWH and HIV-uninfected individuals. We hypothesized that PWH would have a greater burden of intracranial arterial wall enhancement compared with HIV-uninfected individuals.

METHODS

We recruited participants prior to randomization in a single-center parent trial evaluating the impact of alirocumab, a PCSK9 inhibitor, on cardiovascular risk in PWH (EPIC-HIV, NCT03207945). Inclusion criteria for the EPIC-HIV study include age 40 years or older, on stable antiretroviral therapy (ART) with undetectable plasma viral load, and at moderate

to high cardiovascular risk, defined as: history of cardiovascular disease or of at least one cardiometabolic risk factor (e.g., hypertension, hyperlipidemia, diabetes mellitus, current smoker). Participants with a stroke or central nervous system infection (e.g., meningitis, encephalitis) within the past 90 days, or who had signs or symptoms of acute stroke at the time of imaging, were excluded. Age-matched HIV-uninfected individuals, all of whom met eligibility criteria, were friends and family of PWH or were recruited through flyers. Participants were enrolled between September 2018 and January 2021. Written informed consent was obtained from all participants.

Participants underwent an intracranial TOF MRA and 3D high-resolution variable flip angle black blood post-contrast VW-MRI (CUBE) on a GE 3T Discovery scanner. Two neuroradiologists (AC and JN) blinded to HIV status reviewed the bilateral internal carotid arteries; anterior, middle, and posterior cerebral arteries; vertebral arteries; and the basilar artery and quantified the number of arteries with wall enhancement, which was the primary outcome. In addition, for each enhancing artery, the following were characterized: 1) eccentric versus concentric pattern and extent (i.e., short versus long-segment) of enhancement and 2) presence of associated luminal narrowing on MRA.

We compared demographic and clinical characteristics between PWH and HIV-uninfected individuals using Student's t, Chi-square or Fisher's exact test. We used Poisson and logistic regression models to investigate the unadjusted association of HIV with the number of enhancing arteries and presence of any arterial wall enhancement. In multivariable Poisson models of the association between HIV infection and the number of enhancing arteries, we adjusted for (1) age, natal sex, and race and then for (2) age, natal sex, race, and individual cardiometabolic risk factors, or any covariates that differed between PWH and HIV-uninfected individuals. To investigate the association between HIV and specific characteristics of arterial wall enhancement (e.g., eccentric versus concentric enhancement), we used mixed effects logistic regression models, which included a random subject effect to account for within-person correlation, as some participants had more than one enhancing artery. P values were two-sided with 0.05 considered statistically significant. Statistical analyses were performed using Stata 12.1 (College Station, TX, USA).

RESULTS

Of 46 participants, 33 were PWH. Age [mean 59 years, standard deviation (SD) 8 years] and sex (91% assigned male sex at birth) were similar between groups. We observed a trend toward a greater proportion of HIV-uninfected individuals identifying as Black (31%) or other race/ethnicity (23%) compared with PWH (15% and 6%, respectively; p=0.073). Of cardiometabolic risk factors and health-related behaviors, current statin use (79% versus 46%, p=0.030) and any marijuana use (88% versus 23%, p=<0.001) were significantly more prevalent in PWH compared with HIV-uninfected individuals. The majority of PWH (82%) were on an integrase strand transfer inhibitor-based regimen. Only 18% of PWH were on abacavir, and 21% were on a protease inhibitor. Among PWH, mean CD4 count was 547 cells/mm^3 (SD 201 cells/mm^3).

PWH had a greater mean number of enhancing intracranial arteries (1.52, SD 1.44) compared with HIV-uninfected individuals (0.38, SD 0.87), which translated to 3.94 times as many enhancing arteries in PWH (95% CI 1.57 to 9.88, p=0.003). PWH had 8.66-fold higher odds (95% CI 1.21 to 61.81, p=0.031) of having one or more enhancing arteries compared with HIV-uninfected individuals. The greater burden of arterial wall enhancement in PWH compared with HIV-uninfected individuals remained statistically significant after adjusting for age, natal sex, race, and individual cardiometabolic factors or covariates that differed by HIV status (Table). Among PWH, we did not observe a significant association of abacavir use (rate ratio 1.04, 95% CI 0.49–2.18, p=0.92) or protease inhibitor use (rate ratio 0.68, 95% CI 0.32–1.45, p=0.31) with the burden of arterial wall enhancement.

The pattern of wall enhancement for the majority of enhancing arteries was eccentric (76%) and short-segment (93%). Over two-thirds (69%) of arteries with wall enhancement did not have associated luminal narrowing on TOF MRA. In mixed effects models that accounted for correlations between multiple enhancing arteries within participants, we did not detect a statistically significant difference in the pattern of enhancement [odds ratio (OR) for eccentric wall enhancement for PWH compared with HIV-uninfected individuals was 11.25, 95% CI 0.07–1923.08, p=0.36] or presence of associated luminal narrowing (OR for PWH compared with HIV-uninfected individuals was 0.40, 95% CI 0.01–14.16, p=0.62) by HIV status.

DISCUSSION

In this cross-sectional study, persons with ART-treated, virologically suppressed HIV infection had a greater burden of primarily eccentric, short-segment intracranial arterial wall enhancement compared with HIV-uninfected individuals, independent of age, natal sex, race, and cardiometabolic risk factors. Furthermore, luminal imaging with TOF MRA underestimated intracranial arterial disease in over two-thirds of vessels that demonstrated arterial wall enhancement on VW-MRI (Figure). This finding is in line with studies from the general population that have demonstrated superiority of VW-MRI in the detection of non-stenotic ICAD.[7, 9, 10] Because MRA and CTA primarily capture luminal deficits, ICAD may go undetected on these imaging modalities, especially if atherosclerotic vessels have undergone ‘positive remodeling’ that does not affect the caliber of the vessel.

VW-MRI enhancement characteristics can help to differentiate between etiologies of intracranial arterial disease. While there is overlap between the patterns of enhancement observed in different intracranial arterial pathologies, eccentric short-segment vessel wall enhancement is predominantly seen in ICAD, whereas concentric, relatively homogeneous long-segment enhancement is more common in intracranial vasculitis. The predominance of eccentric, short-segment enhancement suggests that ICAD was the prevalent arterial pathology in this study of participants at moderate to high cardiovascular risk.

Our findings should be interpreted in the context of several limitations. First, few women were included, which precludes generalization of our findings to women with HIV infection. Second, the race/ethnicity distribution was dissimilar between groups, with a trend toward more non-White HIV-uninfected participants. However, as non-White populations have

higher rates of ICAD,[6] this would have biased toward the null hypothesis of no difference in the burden of arterial wall enhancement by HIV status. Third, although the observed associations between HIV and arterial wall enhancement persisted after accounting for group differences in the prevalence of several factors, the modest sample size prohibited us from adjusting for multiple variables concurrently in our models.

In conclusion, we found a greater burden of intracranial arterial wall enhancement in PWH with ART-treated, virologically suppressed infection compared with HIV-uninfected individuals. A comprehensive evaluation of cerebrovascular risk in PWH should incorporate assessment of intracranial large artery disease, including high-resolution VW-MRI as an adjunct to traditional luminal imaging when feasible.

ACKNOWLEDGEMENTS

We are grateful to the study participants and research staff, without whom this work would not have been possible. Many thanks also to Dr. Peter Bacchetti for his statistical mentorship. This research was supported by NINDS/NIH K23NS105575 (FCC), NHLBI/NIH R01HL149787 (JN), and NIAID/NIH K24AI112393 (PYH).

Funding:

This research was supported by NINDS/NIH K23NS105575 (FCC), NHLBI/NIH R01HL149787 (JN), and NIAID/NIH K24AI112393 (PYH).

REFERENCES

1. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. Comparison of Ischemic Stroke Incidence in HIV-Infected and Non-HIV-Infected Patients in a US Health Care System. J Acquir Immune Defic Syndr. 2012;60:351–358. [PubMed: 22580566]
2. Chow FC, Price RW, Hsue PY, Kim AS. Greater Risk of Stroke of Undetermined Etiology in a Contemporary HIV-Infected Cohort Compared with Uninfected Individuals. J Stroke Cerebrovasc Dis. 2017;26:1154–1160. [PubMed: 28262563]
3. Benjamin LA, Allain TJ, Mzinganjira H, et al. The Role of Human Immunodeficiency Virus–Associated Vasculopathy in the Etiology of Stroke. J Infect Dis 2017;216:545–553. [PubMed: 28931222]
4. Moulignier A, Savatovsky J, Assoumou L, et al. , Microvascular Brain Retina and Kidney (MicroBREAK) Study Group. Silent Cerebral Small-Vessel Disease Is Twice as Prevalent in Middle-Aged Individuals With Well-Controlled, Combination ART-Treated HIV Than in HIV-Uninfected Individuals. Clin Infect Dis. 2018;66:1762–1769. [PubMed: 29244126]
5. Sanford R, Strain J, Dadar M, Maranzano J, et al. HIV infection and cerebral small vessel disease are independently associated with brain atrophy and cognitive impairment. AIDS. 2019;33:1197–1205. [PubMed: 30870193]
6. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large Artery Intracranial Occlusive Disease: A Large Worldwide Burden but a Relatively Neglected Frontier. Stroke. 2008;39:2396–2399. [PubMed: 18535283]
7. Song JW, Obusez EC, Raymond SB, Rafla SD, Schaefer PW, Romero JM. Vessel Wall MRI Added to MR Angiography in the Evaluation of Suspected Vasculopathies. J Neuroimaging. 2019;29:454–457. [PubMed: 30761654]
8. Mossa-Basha M, Shibata DK, Hallam DK, et al. Added Value of Vessel Wall Magnetic Resonance Imaging for Differentiation of Nonocclusive Intracranial Vasculopathies. Stroke. 2017;48:3026–3033. [PubMed: 29030476]
9. Natori T, Sasaki M, Miyoshi M, Ohba H, Katsura N, Yamaguchi M, Narumi S, Kabasawa H, Kudo K, Ito K, Terayama Y. Evaluating Middle Cerebral Artery Atherosclerotic Lesions in Acute

Ischemic Stroke Using Magnetic Resonance T1-weighted 3-Dimensional Vessel Wall Imaging. J Stroke Cerebrovas Dis. 2014;23:706–711.

10. Klein IF, Lavallée PC, Schouman-Claeys E, Amarenco P. High-resolution MRI identifies basilar artery plaques in paramedian pontine infarct. Neurology 2005;64:551–552. [PubMed: 15699395]

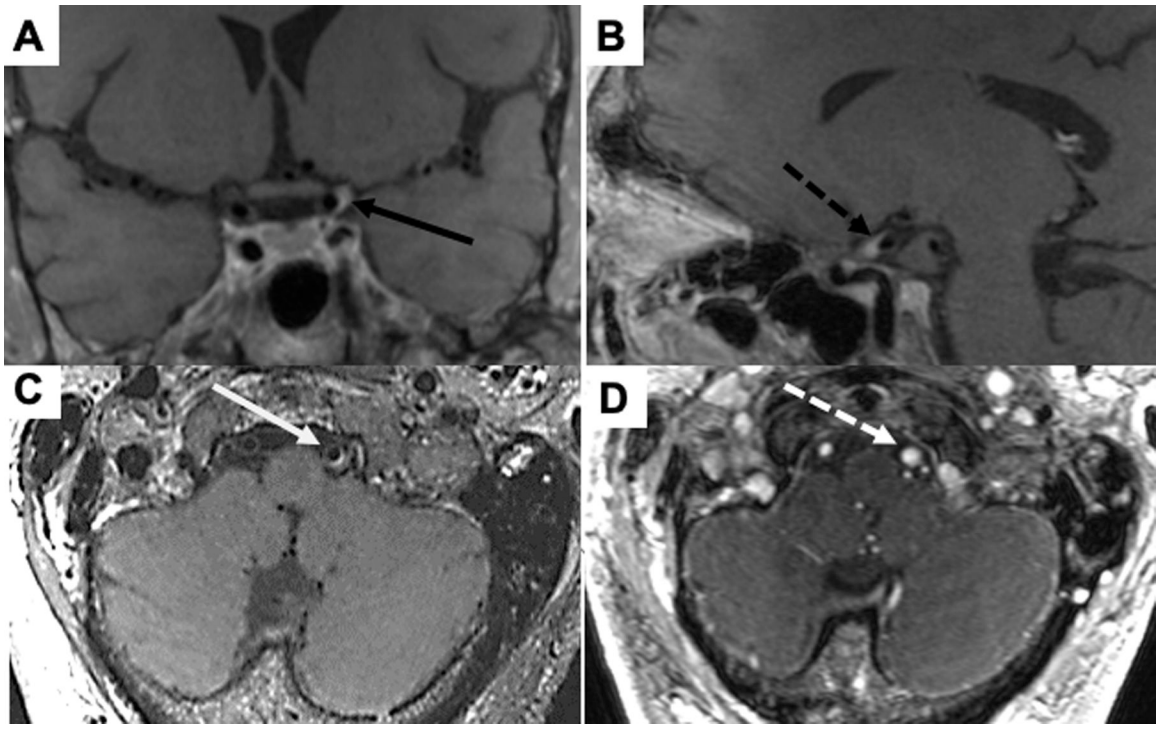

Figure:

Intracranial arterial wall enhancement on vessel wall MRI (VW-MRI) in participants with HIV infection. (A) Coronal (solid black arrow) and (B) sagittal (dashed black arrow) views of eccentric wall enhancement of the left internal carotid artery of a participant with HIV infection. (C) Eccentric wall enhancement (solid white arrow) of the left vertebral artery with preserved caliber of the vessel on VW-MRI in another participant with HIV. This finding would have gone undetected without VW-MRI, as (D) time-of-flight magnetic resonance angiography showed normal caliber with no luminal narrowing (dashed white arrow).

Table:

Burden of intracranial arterial wall enhancement in PWH versus HIV-uninfected individuals

	Estimated fold-effect of HIV infection on number of enhancing intracranial arteries (95% CI)	P-value
Model 1: Unadjusted	3.94 (1.57–9.88)	0.003
Model 2: Age, sex, race	3.88 (1.46–10.29)	0.006
Model 2 + hypertension	3.83 (1.43–10.26)	0.007
Model 2 + anti-hypertensive use	4.15 (1.52–11.35)	0.006
Model 2 + dyslipidemia	3.67 (1.36–9.91)	0.010
Model 2 + statin use	3.77 (1.41–10.11)	0.008
Model 2 + diabetes mellitus	3.74 (1.39–10.05)	0.009
Model 2 + CHD	3.83 (1.43–10.28)	0.008
Model 2 + ever smoker	3.86 (1.41–10.52)	0.008
Model 2 + ever marijuana use	3.44 (1.14–10.40)	0.029