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Effects of Early Human Immunodeficiency Virus Infection on Cerebral White Matter Blood Flow Autoregulation

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SUMMARY

Blood flow autoregulation in cerebral white matter was measured before and after acute nicardipine-induced changes in mean arterial pressure of 10–21% in 21 treatment naïve HIV-positive adults and 32 controls. The Autoregulatory Index (-%CBF change/% MAP change) was not different at baseline (p= 0.71) or after one year of treatment (n=11, p=0.17). We found no autoregulatory defect to explain the increased stroke risk or the development of cerebral white damage in people with HIV.

Keywords

Autoregulation; cerebral blood flow; human immunodeficiency virus; white matter; stroke

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AUTHOR CONTRIBUTIONS

1. Souvik Sen MD: Design, implementation, conduct of the study, data analysis and manuscript preparation
2. Hongyu An PhD: Design, implementation, conduct of neuroimaging, data analysis and manuscript writing of neuroimaging sections.
3. Jonathan Oakes BA: Recruitment of participants, research coordination, study conduct, data collection and monitoring, review of manuscript.
4. Joseph Eron MD: Recruitment and design of research methods, implementation, data analysis and review of manuscript.
5. Kevin Robertson PhD: Design of the research study, implementation of neuropsychological assessment, data analysis and initial draft of manuscript.
6. William J. Powers MD: Design, implementation, conduct of the study, data analysis and manuscript preparation

DISCLOSURES

The authors declare that there are no conflicts of interest

INTRODUCTION

An increased risk of ischemic stroke independent of traditional vascular risk factors has been reported in people with HIV (PWHIV). [1–3] White matter (WM) hyperintensities on neuroimaging indicating tissue damage are more common in PWHIV than in age matched controls, although not in all series. [1, 4–6] The mechanism of these have not been fully elucidated. [1, 7]

Normally, the physiological mechanism of cerebral autoregulation maintains cerebral blood flow (CBF)) within a narrow range by compenatory arteriolar vasodilation during 20–30% reductions in mean arterial pressure (MAP), thus precventing ischemic damage. [8–10] In PWHIV, impaired cerebral vasodilatory responses to carbon dioxide and acetazolamide have been reported. [11, 12] While these studies do not provide specific data on WM vascular function nor on the autoregulatory vasodilatory responses to changes in MAP, they suggest that impaired white matter autoregulation resulting in ischecmic damage may be important in the cerebral pathology of HIV.

MATERIALS AND METHODS

HIV-positive adults without evidence of AIDS-defining illness who had not yet begun ART were recruited through the University of North Carolina Infectious Diseases Clinic. HIV-negative controls matched by gender and age (±2 years) were recruited through IRB approved local, newspaper, and email listserv advertisements and flyers. Exclusion criteria are described in a previous publication [13].

CBF was measured using pseudo-continuous arterial spin labeling (pCASL) at ambient MAP and after acute MAP reduction. [14, 15] [16] MAP was lowered with intravenous nicardipine infusion with a target of ≥10% but no more than 15% reduction to a maximum dose of 15 mg/hr. CBF measurements were repeated in the PWHIV after 12 months of ART. Image analysis was performed as described previously. [17]

Autoregulation was measured by the Autoregulatory Index (AI) separately for WM and GM. AI= −(%Change in CBF)/(%Change in MAP). [18, 19]

The primary analysis was the comparison of WM AI in control participants to PWHIV at baseline and after 12 months of ART with the threshold for statistical significance set at p= 0.05 using the single-step multiple contrast test procedure (mctp “Dunnett”). [20] A secondary analysis of GM AI was also performed. The p-values for the secondary analyses are presented without correction for multiple comparisons and should be interpreted with this limitation. Statistical calculations were performed using R 4.0.2. (www.r-project.org).

This study was approved by the University of North Carolina Chapel Hill Institutional Review Board. All participants provided written informed consent before participating.

RESULTS

Of 46 control participants enrolled, 32 achieved target MAP reduction. Of 41 PWHIV enrolled, 21 achieved target MAP reduction at baseline. Final nicardipine doses were 9.1±4.4 mg/hr in the 32 controls and 8.7±4.2 mg/hr in the 21 PWHIV (p=0.76). At 1 year, 30 PWHIV returned. 12 achieve target MAP reduction. One was eliminated as an outlying value, leaving 11 for analysis. Four PWHIV were in both baseline and 1-year groups.

Ages were 29.6±7.7 years in controls, 27.5±5.6 years in baseline PWHIV, and 32.2±10.2 years in 1-year PWHIV groups. Since 19/21 of the PWHIV participants were men, the control group is mostly (30/32) men as well. At 1 year, 11/11 of the PWHIV were men. Groups were well-matched except there were more smokers in the PWHIV groups at baseline (52%) and one year (82%) as compared to controls (22%). Hypertension was present in 1 (3%) of controls, 3 (14%) of baseline PWHIV and 2 (19%) of 1-year PWHIV. Diabetes was present in 0 controls, 1 (5%) of baseline PWHIV and 1 (9%) of 1-year PWHIV. Hyperlipidemia was present in 1(3%) of controls, 1(5%) of baseline PWHIV and 1(9%) of 1-year PWHIV. In baseline PWHIV participants, median CD4 counts were 473 [interquartile range (IQR) 362-606] cells/mm^3 and median viral copies were 38445 (IQR 6584-114695)/mL. At 1 year all 11 of the PWHIV participants were prescribed multi-drug highly active anti-retroviral therapy. Median CD4 counts were 798 (IQR 501-851) cells/mm^3 and median viral copies were 39 (IQR 39-44)/mL.

In the primary analysis, WM AI in the PWHIV group was not significantly different from controls at baseline (mean difference 0.29, 95% CI −0.64 to 1.23, p= 0.71) or at one year (mean difference 0.87, 95% CI −0.29 to 2.03, p=0.17) (Table). Effect sizes (Cohen's d) associated with the lower limits of the 95% CI of the differences for WM AI for the two pairwise comparisons are −0.49 for the former and −0.19 for the latter. These exclude with 95% confidence effect sizes for defective (more negative) AI in the PWHIV that are than medium or more (< −0.50) and small or more (< −0.20) respectively. [21]

GM AI in the PWHIV group at baseline or at one year was not different from controls (p= 0.67 and 0.60. Data not shown).

DISCUSSION

Strengths of our study include quantitative regional measurements of CBF specifically in WM, which is commonly affected in PWHIV. [22] We assessed the stability of CBF to changes in MAP, which is directly relevant to the potential causation of naturally occurring cerebral ischemic damage, rather to changes carbon dioxide and acetazolamide administration, which have unclear clinical significance. We studied both PWHIV when treatment-naive and after 12months on ART to assess any effect of ART.

The major limitation of our study is that almost all of the participants were men. We studied PWHIV early in the course of disease with minimal or no MRI WM damage, so these results do not apply to PWHIV with longer duration of disease, more severe WM damage or longer treatment with ART. We chose a target reduction in MAP of 10–15% of baseline to

remain within the normal autoregulatory range. [23, 24] We cannot determine if the limits of autoregulation below these levels of MAP are different in PWHIV.

In conclusion, the stability of CBF in response to these MAP changes was similar between PWHIV cases and controls and remained so after 12 months of ART. We found no evidence of a defect in autoregulation to explain the high risk of ischemic stroke documented in other studies or the development of WMH in PWHIV.

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REFERENCES

1. Moulignier A, Costagliola D. Metabolic Syndrome and Cardiovascular Disease Impacts on the Pathophysiology and Phenotype of HIV-Associated Neurocognitive Disorders. Curr Top Behav Neurosci 2020.
2. Marcus JL, Leyden WA, Chao CR, Chow FC, Horberg MA, Hurley LB, et al. HIV infection and incidence of ischemic stroke. AIDS 2014; 28(13):1911–1919. [PubMed: 24937309]
3. Nguyen I, Kim AS, Chow FC. Prevention of stroke in people living with HIV. Prog Cardiovasc Dis 2020; 63(2):160–169. [PubMed: 32014514]
4. Moulignier A, Savatovsky J, Assoumou L, Lescure FX, Lamirel C, Godin O, et al. Silent Cerebral Small-Vessel Disease Is Twice as Prevalent in Middle-Aged Individuals With Well-Controlled, Combination Antiretroviral Therapy-Treated Human Immunodeficiency Virus (HIV) Than in HIV-Uninfected Individuals. Clin Infect Dis 2018; 66(11):1762–1769. [PubMed: 29244126]
5. Haddow LJ, Sudre CH, Sokolska M, Gilson RC, Williams IG, Golay X, et al. Magnetic Resonance Imaging of Cerebral Small Vessel Disease in Men Living with HIV and HIV-Negative Men Aged 50 and Above. AIDS Res Hum Retroviruses 2019; 35(5):453–460. [PubMed: 30667282]
6. Sanford R, Strain J, Dadar M, Maranzano J, Bonnet A, Mayo NE, et al. HIV infection and cerebral small vessel disease are independently associated with brain atrophy and cognitive impairment. AIDS 2019; 33(7):1197–1205. [PubMed: 30870193]
7. Jensen BK, Roth LM, Grinspan JB, Jordan-Sciutto KL. White matter loss and oligodendrocyte dysfunction in HIV: A consequence of the infection, the antiretroviral therapy or both? Brain Res 2019; 1724:146397. [PubMed: 31442414]
8. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Rev 1990; 2(2):161–192. [PubMed: 2201348]
9. Moerman A, De Hert S. Why and how to assess cerebral autoregulation? Best Pract Res Clin Anaesthesiol 2019; 33(2):211–220. [PubMed: 31582100]
10. Claassen J, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev 2021; 101(4):1487–1559. [PubMed: 33769101]
11. Brilla R, Nabavi DG, Schulte-Altedorneburg G, Kemeny V, Reichelt D, Evers S, et al. Cerebral vasculopathy in HIV infection revealed by transcranial Doppler: A pilot study. Stroke 1999; 30(4):811–813. [PubMed: 10187884]
12. Chow FC, Boscardin WJ, Mills C, Ko N, Carroll C, Price RW, et al. Cerebral vasoreactivity is impaired in treated, virally suppressed HIV-infected individuals. AIDS 2016; 30(1):45–55. [PubMed: 26372478]

13. Sen S, An H, Sollman M, Oakes J, Eron J, Robertson K, et al. Reduction in cerebral oxygen metabolism in subcortical regions may be a biomarker of cognitive decline in people living with human immunodeficiency virus. Eur J Neurol 2022; 29(4):1062–1074. [PubMed: 34821434]

14. Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. Magn Reson Med 2008; 60(6):1488–1497. [PubMed: 19025913]

15. Wu WC, Jiang SF, Yang SC, Lien SH. Pseudocontinuous arterial spin labeling perfusion magnetic resonance imaging--a normative study of reproducibility in the human brain. Neuroimage 2011; 56(3):1244–1250. [PubMed: 21385620]

16. Wu WC, Fernandez-Seara M, Detre JA, Wehrli FW, Wang J. A theoretical and experimental investigation of the tagging efficiency of pseudocontinuous arterial spin labeling. Magn Reson Med 2007; 58(5):1020–1027. [PubMed: 17969096]

17. Powers WA H; Oakes J; Eron J; Robertson K; Sen S Autoregulation of White Matter Cerebral Blood Flow to Arterial Pressure Changes in Normal Subjects. J Neurol Disord Stroke 2021; 8(3).

18. Jones SC, Radinsky CR, Furlan AJ, Chyatte D, Qu Y, Easley KA, et al. Variability in the magnitude of the cerebral blood flow response and the shape of the cerebral blood flow-pressure autoregulation curve during hypotension in normal rats [corrected]. Anesthesiology 2002; 97(2):488–496. [PubMed: 12151941]

19. Dirnagl U, Pulsinelli W. Autoregulation of cerebral blood flow in experimental focal brain ischemia. J Cereb Blood Flow Metab 1990; 10:327–336. [PubMed: 2329121]

20. Konietschke F, Placzek M, Schaarschmidt F, Hothorn LA. nparcomp: An R Software Package for Nonparametric Multiple Comparisons and Simultaneous Confidence Intervals. J Stat Softw 2015; 64(9).

21. Sedgwick P Effect Sizes. BMJ 2012; 345:e7370.

22. Eggers C, Arendt G, Hahn K, Husstedt IW, Maschke M, Neuen-Jacob E, et al. HIV-1-associated neurocognitive disorder: epidemiology, pathogenesis, diagnosis, and treatment. J Neurol 2017; 264(8):1715–1727. [PubMed: 28567537]

23. Symon L, Pasztor E, Dorsch NW, Branston NM. Physiological responses of local areas of the cerebral circulation in experimental primates determined by the method of hydrogen clearance. Stroke 1973; 4(4):632–642. [PubMed: 4723693]

24. Ferrari M, Wilson DA, Hanley DF, Traystman RJ. Effects of graded hypotension on cerebral blood flow, blood volume, and mean transit time in dogs. Am J Physiol 1992; 262(6 Pt 2):H1908–H1914. [PubMed: 1621847]

Table:

White Matter Autoregulatory Index (WM AI), mean arterial pressure (MAP, mm Hg) and white matter cerebral blood flow (WM CBF, mL $100g^{-1}$ min^{-1}) in controls and people with the human immunodeficiency virus (PWHIV) at baseline and at one year. Mean ± standard deviation

	Controls (N=32)	**PWHIV Baseline (N=21)**	**p-value vs Controls[a]**	**PWHIV 1 year (N=11)**	**p-value vs Controls[a]**
WM AI	**−0.65±1.26**	**−0.36±1.40**	**0.71** [a]	**0.22±2.05**	**0.17** [a]
MAP					
Initial	85.0±9.5	86.2±9.0	0.84	88.6±9.0	0.26
Reduced	73.2±7.9	74.6±7.5	0.83	76.7±5.7	0.09
Change	−13.8±2.6%	−13.4±2.9%	0.78	−13.2±2.6%	0.63
Range	−10 to −20%	−10 to −21%		−10 to −19%	
WM CBF					
Initial MAP	30.4±7.6	31.0±8.6	0.93[a]	30.8±9.3	0.94[a]
Reduced MAP	28.2±9.0	28.9±8.5	0.77[a]	31.3±8.6	0.24[a]
p-value initial vs. reduced	***0.02*** [b]	0.09[c]		0.76[c]	

[a] mctp “Dunnett”

[b] Paired Wilcoxon signed rank test

[c] Paired t-test