Austin Journal of Cerebrovascular Disease & Stroke

Austin Publishing Group

Open Access Full Text Article

Perspective

Cerebral Small Vessel Disease in HIV-1 Infected Individuals

Soontornniyomkij V*
Department of Psychiatry, University of California San Diego, USA

***Corresponding author:** Soontornniyomkij V, Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-2623, USA, Tel: 858-822-4546; Fax: 858-534-4484; Email: vsoontor@ucsd.edu

Received: August 12, 2014; **Accepted:** August 15, 2014; **Published:** August 19, 2014

Perspective

While HIV-associated dementia is rare in the current era of highly active antiretroviral therapy (HAART), the milder forms of HIV-associated neurocognitive disorders (HAND), asymptomatic neurocognitive impairment and mild neurocognitive disorder, are common [1,2]. Patients could develop HAND even when their systemic HIV infection and immune function remain under control [2-4]. Recent postmortem brain studies suggest that HAND is not necessarily associated with HIV encephalitis [5-7] and may be related to various comorbid factors such as long-term exposure to antiretroviral medications [8], age-related cerebrovascular and neurodegenerative changes [9,10], co-infection with hepatitis C virus, and substance use (e.g., methamphetamine) [11,12].

Previous studies suggest that HIV-infected individuals are at increased risk of ischemic cerebrovascular diseases, potentially caused by infective vasculitis, brain opportunistic diseases, hypercoagulopathy, cardiac embolism, or HIV infection itself [13-20]. Included among a variety of brain vessel pathologies found in this context is cerebral small vessel disease (CSVD), known in histopathological terminology as arteriolosclerosis: concentric intramural hyalinization of small arteries or arterioles [15,17,19]. In the general population, CSVD is associated with diabetes, hypertension, and older age [21], although the underlying mechanisms are still unknown. In patients who receive HAART, particular antiretroviral drugs may directly cause injury to vessel walls or indirectly induce metabolic abnormalities (e.g., dyslipidemia and insulin resistance) that accelerate the development of atherosclerotic large vessel disease [22,23]. Nonetheless, the potential impact of HAART exposure on the development of ischemic cerebrovascular diseases, including CSVD, remains controversial [14,15,18,19,24-26]. In a community-based study [27], the presence of punctate white matter lesions (hyperintensities) on magnetic resonance imaging (MRI) was found to be associated with older age and higher systolic blood pressure; furthermore, there was a trend toward the direct association between white matter lesions and HAART exposure. Whereas in the general population white matter lesions detected on MRI are thought to represent ischemic lesions caused by CSVD [28], the similar lesions in HIV-infected individuals may also reflect foci of HIV-associated or inflammatory white matter injury [29-32].

We propose that chronic toxic effects of antiretroviral drugs on the cell components of vessel walls can contribute to CSVD, which may be one of the key underpinnings of HAND. More severe forms of CSVD may lead to neurocognitive impairment via cerebral blood flow restriction sufficient to produce white matter lesions and microinfarcts. In mild CSVD, neurocognitive compromise may be associated with disturbance of cerebrovascular autoregulation and deficiency in functional hyperemia, which together could impair new protein synthesis in neurons required for synaptic plasticity and memory formation [21,33-36].

Recently, we have conducted a cross-sectional clinico-pathological analysis using postmortem brain specimens obtained from the California NeuroAIDS Tissue Network and reported that exposure to protease inhibitor (PI)-based HAART might increase the risk of CSVD in the forebrain white matter [37]. Specifically, using multivariable logistic regression analyses we found direct associations between PI-based HAART exposure and higher likelihood of both mild and moderate/severe CSVD after statistically adjusting for diabetes. Moderate/severe CSVD was associated with diabetes after statistically adjusting for HAART exposure, older age (i.e., 50 years or older), and hypertension. Importantly, we found that mild CSVD was associated with HAND even after statistically adjusting for vessel mineralization, HIV encephalitis, microglial nodular lesions, white matter lesions, or older age. While the mechanisms remain to be delineated, it is possible that particular drug components of PI-based HAART may be toxic to the cellular components of cerebral small vessels, such as vascular endothelial cells and smooth muscle cells, leading to vessel wall degeneration. It is also possible that some drugs in PI-based HAART contribute indirectly to CSVD by inducing metabolic abnormalities such as dyslipidemia and insulin resistance, as they have been implicated in the premature development of atherosclerotic large vessel disease [22, 23].

It is important to note that different antiretroviral drugs even in the same class may carry different degrees of toxicity on cerebral vessels. This matter can be addressed using experimental animals [38] and *in vitro* cell systems [39]. Also, the toxic effects of antiretroviral drugs may vary with the duration of drug use and the rate of drug metabolism in individual patients.

Vessel mineralization (defined histopathologically as intramural deposition of basophilic amorphous material in small and medium-sized arteries) found primarily in the globus pallidus was consistently reported in pre-HAART HIV autopsy cohorts [40,41]. In our recent study [37], in contrast to CSVD, there was no significant association between vessel mineralization and HAART exposure. In addition, the presence of vessel mineralization was not significantly associated with that of CSVD. These findings suggest that vessel mineralization may be pathophysiologically different from CSVD and mediated by the HIV-related effects on vessel walls in a brain region-specific manner.

Citation: Soontornniyomkij V. Cerebral Small Vessel Disease in HIV-1 Infected Individuals. Austin J Cerebrovasc Dis & Stroke. 2014;1(3): 1011.

While the pathophysiology of atherosclerotic large vessel disease has been studied extensively with regard to the roles of inflammation and vascular cell proliferation [42-44], the underlying mechanisms of arteriolosclerosis are largely unexplored other than the identification of associated risk factors (i.e., diabetes, hypertension, older age) [21]. For future research directions, it is of interest to investigate the molecular mechanisms of drug toxicity (e.g., antiretroviral drugs, methamphetamine) to the cell components of cerebral vessels, protective effects of potential rescue agents (e.g., antioxidants, phytoestrogens), and identification of potential biomarkers for CSVD in body fluids or more accessible peripheral tissues. For instance, specific antiretroviral drugs or drug combinations may affect the integrity and function of cerebral vessels by inducing premature senescence of vascular endothelium and smooth muscle cells [39,45]. The ritonavir–lopinavir PI combination could induce premature aging of endothelial cells by mechanisms involving oxidative stress and dysregulation in the maturing process of lamin-A (an intermediate filament protein constituting the structural scaffold for the nuclear lamina) [39].

References

1. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011; 17: 3-16.

2. Nath A, Schiess N, Venkatesan A, Rumbaugh J, Sacktor N, McArthur J, et al. Evolution of HIV dementia with HIV infection. Int Rev Psychiatry. 2008; 20: 25-31.

3. Brew BJ. Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. AIDS. 2004; 18 Suppl 1: S75-78.

4. Cysique LA, Brew BJ. Prevalence of non-confounded HIV-associated neurocognitive impairment in the context of plasma HIV RNA suppression. J Neurovirol. 2011; 17: 176-183.

5. Everall I, Vaida F, Khanlou N, Lazzaretto D, Achim C, Letendre S, et al. Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. J Neurovirol. 2009; 15: 360-370.

6. Gelman BB, Chen T, Lisinicchia JG, Soukup VM, Carmical JR, Starkey JM, et al. The National NeuroAIDS Tissue Consortium brain gene array: two types of HIV-associated neurocognitive impairment. PLoS One. 2012; 7: e46178.

7. Gelman BB, Lisinicchia JG, Morgello S, Masliah E, Commins D, Achim CL, et al. Neurovirological correlation with HIV-associated neurocognitive disorders and encephalitis in a HAART-era cohort. J Acquir Immune Defic Syndr. 2013; 62: 487-495.

8. Marra CM, Zhao Y, Clifford DB, Letendre S, Evans S, Henry K, et al. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. AIDS. 2009; 23: 1359-1366.

9. Soontornniyomkij V, Achim CL. Aging. Gendelman HE, editor. In: The Neurology of AIDS. Oxford University Press. 2012; 567-580.

10. Soontornniyomkij V, Moore DJ, Gouaux B, Soontornniyomkij B, Tatro ET, Umlauf A. Cerebral Î²-amyloid deposition predicts HIV-associated neurocognitive disorders in APOE Îµ4 carriers. AIDS. 2012; 26: 2327-2335.

11. Cherner M, Letendre S, Heaton RK, Durelle J, Marquie-Beck J, Gragg B, et al. Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. Neurology. 2005; 64: 1343-1347.

12. Letendre SL, Cherner M, Ellis RJ, Marquie-Beck J, Gragg B, Marcotte T, et al. The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance: biological correlates of disease. AIDS. 2005; 19 Suppl 3: S72-78.

13. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA, et al. 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.

14. Cruse B, Cysique LA, Markus R, Brew BJ. Cerebrovascular disease in HIV-infected individuals in the era of highly active antiretroviral therapy. J Neurovirol. 2012; 18: 264-276.

15. Ortiz G, Koch S, Romano JG, Forteza AM, Rabinstein AA. Mechanisms of ischemic stroke in HIV-infected patients. Neurology. 2007; 68: 1257-1261.

16. Ovbiagele B, Nath A. Increasing incidence of ischemic stroke in patients with HIV infection. Neurology. 2011; 76: 444-450.

17. Connor MD, Lammie GA, Bell JE, Warlow CP, Simmonds P, Brettle RD, et al. Cerebral infarction in adult AIDS patients: observations from the Edinburgh HIV Autopsy Cohort. Stroke. 2000; 31: 2117-2126.

18. Rasmussen LD, Engsig FN, Christensen H, Gerstoft J, Kronborg G, Pedersen C, et al. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. AIDS. 2011; 25: 1637-1646.

19. Benjamin LA, Bryer A, Emsley HC, Khoo S, Solomon T, Connor MD, et al. HIV infection and stroke: current perspectives and future directions. Lancet Neurol. 2012; 11: 878-890.

20. Singer EJ, Valdes-Sueiras M, Commins DL, Yong W, Carlson M. HIV stroke risk: evidence and implications. Ther Adv Chronic Dis. 2013; 4: 61-70.

21. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010; 9: 689-701.

22. Grunfeld C. Dyslipidemia and its Treatment in HIV Infection. Top HIV Med. 2010; 18: 112-118.

23. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis. 2010; 201: 318-330.

24. d'Arminio A, Sabin CA, Phillips AN, Reiss P, Weber R, Kirk O, et al. Cardio- and cerebrovascular events in HIV-infected persons. AIDS. 2004; 18: 1811-1817.

25. Corral I, Quereda C, Moreno A, Pérez-Elías MJ, Dronda F, Casado JL, et al. Cerebrovascular ischemic events in HIV-1-infected patients receiving highly active antiretroviral therapy: incidence and risk factors. Cerebrovasc Dis. 2009; 27: 559-563.

26. Worm SW, Kamara DA, Reiss P, Fontas E, De Wit S, El-Sadr W, et al. Evaluation of HIV protease inhibitor use and the risk of sudden death or nonhemorrhagic stroke. J Infect Dis. 2012; 205: 535-539.

27. McMurtray A, Nakamoto B, Shikuma C, Valcour V. Small-vessel vascular disease in human immunodeficiency virus infection: the Hawaii aging with HIV cohort study. Cerebrovasc Dis. 2007; 24: 236-241.

28. Ovbiagele B, Saver JL. Cerebral white matter hyperintensities on MRI: Current concepts and therapeutic implications. Cerebrovasc Dis. 2006; 22: 83-90.

29. Archibald SL, Masliah E, Fennema-Notestine C, Marcotte TD, Ellis RJ, McCutchan JA, et al. Correlation of in vivo neuroimaging abnormalities with postmortem human immunodeficiency virus encephalitis and dendritic loss. Arch Neurol. 2004; 61: 369-376.

30. Miller RF, Lucas SB, Hall-Craggs MA, Brink NS, Scaravilli F, Chinn RJ, et al. Comparison of magnetic resonance imaging with neuropathological findings in the diagnosis of HIV and CMV associated CNS disease in AIDS. J Neurol Neurosurg Psychiatry. 1997; 62: 346-351.

31. Heindel WC, Jernigan TL, Archibald SL, Achim CL, Masliah E, Wiley CA. The relationship of quantitative brain magnetic resonance imaging measures to neuropathologic indexes of human immunodeficiency virus infection. Arch Neurol. 1994; 51: 1129-1135.

32. Filippi CG, Sze G, Farber SJ, Shahmanesh M, Selwyn PA. Regression of HIV encephalopathy and basal ganglia signal intensity abnormality at MR

imaging in patients with AIDS after the initiation of protease inhibitor therapy. Radiology. 1998; 206: 491-498.

33. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci. 2004; 5: 347-360.

34. Farkas E, Luiten PG. Cerebral microvascular pathology in aging and Alzheimer's disease. Prog Neurobiol. 2001; 64: 575-611.

35. Iadecola C. The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. Acta Neuropathol. 2010; 120: 287-296.

36. Moskowitz MA, Lo EH, Iadecola C. The science of stroke: mechanisms in search of treatments. Neuron. 2010; 67: 181-198.

37. Soontornniyomkij V, Umlauf A, Chung SA, Cochran ML, Soontornniyomkij B, Gouaux B. HIV protease inhibitor exposure predicts cerebral small vessel disease. AIDS. 2014; 28: 1297-1306.

38. Reyskens KM, Fisher TL, Schisler JC, O'Connor WG, Rogers AB, Willis MS, et al. Cardio-metabolic effectsof HIV protease inhibitors (lopinavir/ritonavir). PLoS One. 2013; 8: e73347.

39. Lefèvre C, Auclair M, Boccara F, Bastard JP, Capeau J, Vigouroux C, et al. Premature senescence of vascular cells is induced by HIV protease inhibitors: implication of prelamin A and reversion by statin. Arterioscler Thromb Vasc Biol. 2010; 30: 2611-2620.

40. Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV. The neuropathology of AIDS. UCLA experience and review. Am J Pathol. 1986; 124: 537-558.

41. Gray F, Gherardi R, Keohane C, Favolini M, Sobel A, Poirier J, et al. Pathology of the central nervous system in 40 cases of acquired immune deficiency syndrome (AIDS). Neuropathol Appl Neurobiol. 1988; 14: 365-380.

42. Shrestha S, Irvin MR, Grunfeld C, Arnett DK. HIV, inflammation, and calcium in atherosclerosis. Arterioscler Thromb Vasc Biol. 2014; 34: 244-250.

43. Witztum JL, Lichtman AH. The influence of innate and adaptive immune responses on atherosclerosis. Annu Rev Pathol. 2014; 9: 73-102.

44. Johnson JL. Emerging regulators of vascular smooth muscle cell function in the development and progression of atherosclerosis. Cardiovasc Res. 2014.

45. Ragnauth CD, Warren DT, Liu Y, McNair R, Tajsic T, Figg N, et al. Prelamin A acts to accelerate smooth muscle cell senescence and is a novel biomarker of human vascular aging. Circulation. 2010; 121: 2200-2210.

Austin J Cerebrovasc Dis & Stroke - Volume 1 Issue 3 - 2014
ISSN : 2381-9103 | www.austinpublishinggroup.com

Citation: Soontornniyomkij V. Cerebral Small Vessel Disease in HIV-1 Infected Individuals. Austin J Cerebrovasc Dis & Stroke. 2014;1(3): 1011.