Clinical relevance of adverse intracerebral artery remodeling in patients with HIV

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Neurology® 2015;85:1098–1099

Although associated with some alterations of lipid metabolism and development of lipodystrophy, combination antiretroviral therapy (cART) abrogated infections in patients with HIV and improved the quality and expectancy of life.[1] This therapeutic success has allowed the recognition of an association between HIV infection and cardiovascular diseases.[2,3] Long-lived patients with HIV exhibited a marked acceleration of atherosclerosis with an increased risk of acute ischemic events.[3,4] Thus, long-term cardiovascular comorbidities might weaken the relative immune defense benefits induced by cART. It remains unclear if cART directly increases cardiovascular risk or if virus-derived compounds could be responsible for atherogenesis. For instance, recent evidence from clinical trials suggested that viral replication rebound during interruption of cART may provoke a rapid increase of serum levels of cardiovascular risk biomarkers as well as of clinical cardiovascular events.[2,5] Recent results from the Veterans Aging Cohort Study–Virtual Cohort demonstrated an increased risk of cerebral disease, including ischemic stroke, in HIV-positive patients.[6] On the other hand, the Framingham Risk Score for Stroke prediction systematically underestimates the long-term risk of stroke in HIV-positive men, suggesting that many unknown factors might influence the pathophysiology in the cerebral circulation in HIV.[7]

In this issue of *Neurology*®, Gutierrez et al.[8] investigated the potential relationship between intracerebral arterial remodeling and nonembolic cerebral infarction in HIV-positive patients. The authors histologically assessed a very large number of arterial samples (n = 1,878) from a cohort of brain donors, positive (cases, n = 142) and negative (controls, n = 142) for HIV. This appropriately designed study demonstrated that HIV-positive patients were more affected by an inward arterial remodeling (thicker media and arterial wall, accompanied by a reduced lumen-to-wall ratio) as compared to HIV-negative patients. On the other hand, a similar degree of calcification within arteries was observed in the study groups. The independence of these histopathologic features from traditional risk factors suggested that HIV-related compounds or treatments might directly induce an atherosclerosis-like arterial remodeling. Overall, the direct association between HIV infection and the inward remodeling of intracranial arteries represented the most relevant finding by Gutierrez et al. These results further strengthen the well-accepted observation of an accelerated development of atherosclerotic lesions within extracranial arteries in patients with HIV.[9] Gutierrez et al. did not investigate the histologic phenotypes of atherosclerotic lesions in their study. Therefore, we cannot speculate more on potential differences in intraplaque inflammation and structure between HIV-positive and HIV-negative persons. As acknowledged by the authors, the fact that they did not investigate any circulating cardiovascular risk biomarkers that could be selective for patients with HIV represents another important limitation of their observational study.

Gutierrez et al. subsequently focused on potential predictors of cryptogenic cerebral infarction within the HIV-positive arm. Surprisingly, in this preliminary case-control comparison, the authors found high lumen-to-wall ratio was the only predictor of cryptogenic brain infarcts. This reduces the clinical relevance of the previously indicated inward remodeling in patients with HIV. Unlike the inward remodeling associated with vessel stenosis and atherosclerosis, the outward remodeling is characterized by thinning of the media and vessel dilation. Accordingly, the positive correlation between dolichoectasia (an outward extreme phenotype) and high viral load at the time of patient death further stressed this outward remodeling as the main alteration in patients with HIV associated with brain infarction. The fact that the investigators did not explore the potential mechanisms (i.e., HIV infection or treatment) underlying the inward remodeling limits interpretation of this second finding. Further experimental studies will need to evaluate which molecular mechanisms might directly affect vascular function and structure as well as atherogenesis within cerebral arteries.

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

The available scores for cardiovascular risk stratification are ineffective in patients with HIV after the introduction of cART. Emerging risk factors (such as chronic inflammation, HIV-related molecules, senescence related to HIV infection, and chronic cART therapy itself) represent a promising area for research to better assess the dramatically increased cardiovascular risk in patients with HIV. The results by Gutierrez et al. provide an additional tool to understand the potential relationship between HIV infection and cerebral arterial disease, and suggest some structural endpoints (i.e., cerebral arterial remodeling). Further studies are needed to clarify the pathophysiology of HIV-related arterial injury in order to identify therapeutic targets and biomarkers useful for designing tailored preventive strategies in patients with HIV.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures. Go to Neurology.org for full disclosures.

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