SUPPLEMENTAL DATA

e-Methods:

Tissue sources: At the time of autopsy for all individuals, a thorough cerebral and systemic pathological evaluation is carried out. HIV negative controls (N=142) were obtained from the MHBB (N=43), the Macedonian/New York State Psychiatric Institute Brain Collection (N=94) and from the Brain Endowment Bank at University of Miami (N=10). Demographic and clinical data from donors not part of the MHBB were obtained with previously validated neuropsychological interviews, by chart review or self-report (or family-report).[1]

Infarct mechanism ascertainment: Cases with ischemic brain infarcts and history of atrial fibrillation, endocarditis at death, mechanical valves, cardiac thrombi, or cortical infarcts in multiple arterial territories were considered to have cardioembolic infarcts. Infarcts in a subcortical location or a single arterial territory without cardioembolic sources and without evidence of opportunistic infection or lymphoma, but with evidence of atheromas (regardless of fibrous cap thickness) were considered to have non-cardioembolic, atherosclerotic infarcts. Individuals without evidence of brain opportunistic infections or neoplasm, without a source for embolism or large artery atherosclerosis, and without other possible causes for infarct such as hypercoagulable state were considered to have cryptogenic infarcts.

Digital slide processing: Media thickness, LWR, degree of stenosis and luminal diameter were calculated using the areas of each arterial layer and lumen that were automatically obtained with color-based thresholding using Image J software (WS Rasband, ImageJ, U.S. National Institutes of Health, Bethesda, Maryland, USA, imagej.nih gov/ij, 1997–2011) with excellent inter- and intra-reader reliability.[2] Calculations were applied to obtain shrinkage- and folding-corrected areas and diameters of each artery as previously reported.[3] The degree of stenosis was calculated using the method proposed by Glagov et al. [4] Using the histological classification recommended by the American Heart Association, [5] we defined atherosclerosis as the presence of at least a clearly defined atheroma with a fibrotic cap. The presence of atherosclerosis was assessed by one of the authors (JoG). A 5 % sample of arteries was used to calculate inter-rater reliability with a senior neuropathologist (JaG). Using the ratings as a normalized distribution scale, the intraclass correlation coefficient was 0.85 (95% CI 0.76-90, excellent reliability). Categorizing lesions into advanced lesions (atheroma or fibrocalcific plaques) yielded a κ=0.72.

e-discussion:

A novel finding in our study is that intracranial atherosclerosis was more likely among those with a lower nadir CD4 count and a higher CD4 count at the time of death. We interpret these data as evidence that more severe immunosuppression may facilitate atherosclerosis. This is further potentiated when the immune system is subsequently restored in the setting of cART. The mechanism for this potentiation is unclear. Seeding of the artery by opportunistic infections or HIV itself during the period of low nadir CD4 count may create a reservoir for antigenic stimuli. When the immune system is subsequently restored (with the use of antiretrovirals), the wall antigens may stimulate arterial inflammation and enhanced formation of atheroma. This hypothesis is further supported by evidence produced from other groups in extracranial systems. For example, aortic inflammation and increased systemic

macrophage activation have been reported among individuals with well-controlled HIV infection (all were on cART; the mean CD4 count was 641 cells/ul and mean plasma viral load < 48 copies/ml) compared to control groups matched by traditional risk factors. [6] The presence of HIV proteins has been documented in the arterial wall of coronary arteries with atherosclerosis. [7] Alternatively, other infections such as herpes viruses or chlamydia may also be invoked.[8, 9] Whether the native cells of the arterial wall may be infected with HIV and become reservoirs for HIV is another hypothesis must be explored.

Cerebral atherosclerosis and dolichoectasia were associated with half of the cases with brain infarcts in this autopsy series. Arteries with cerebral atherosclerosis and dolichoectasia in HIV were mutually exclusive and with distinct physiopathologies as they relate to HIV. The mechanisms or protein signals that shift the interaction between inflammatory cells, cytokines and arterial cells to produce either phenotype are not clear. It could be argued that atherosclerosis and dolichoectasia are related as it has been suggested in studies of dolichoectasia in non-HIV populations.[10, 11] However, the majority of the pathological reports of dolichoectasia or fusiform aneurysms in cases with HIV have not found significant intima thickening or atherosclerotic lesions. [12, 13] We further confirm this observation reporting here that there was not a single artery with LWR-defined dolichoectasia with evidence of atherosclerosis. Identifying this divergent biology may help understanding better the mechanisms leading to arterial disease and related strokes in this population, and perhaps identify targets for intervention.

e-References:

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