Annexure 01

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Vascular Contributions in Alzheimer's Disease-Related Neuropathological Changes: First Autopsy Evidence from a South Asian Aging Population

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Abstract.
Background: Evidence from various consortia on vascular contributions has been inconsistent in determining the etiology of sporadic Alzheimer's disease (AD).
Objective: To investigate vascular risk factors and cerebrovascular pathologies associated in manifestation of AD-related neuropathological changes of an elderly population.
Methods: Postmortem brain samples from 76 elderly subjects (≥50 years) were used to study genetic polymorphisms, intracranial atherosclerosis of the circle of Willis (IASCW), and microscopic infarcts in deep white matters. From this cohort, 50 brains (≥60 years) were subjected to neuropathological diagnosis using immunohistopathological techniques.

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Results: Besides the association with age, the apolipoprotein E ε4 allele was significantly and strongly associated with Thal amyloid-β phases ≥1 [odds ratio (OR) = 6.76, 95% confidence interval (CI) 1.37–33.45] and inversely with Braak neurofibrillary tangle (NFT) stages ≥III (0.02, 0.0–0.47). Illiterates showed a significant positive association for Braak NFT stages ≥IV (14.62, 1.21–176.73) and a significant negative association for microscopic infarcts (0.15, 0.03–0.71) in deep white matters. With respect to cerebrovascular pathologies, cerebral small vessel lesions (white matter hyperintensities and cerebral amyloid angiopathy) showed a higher degree of associations among them and with AD-related neuropathological changes ($p < 0.05$) compared to large vessel pathology (IASCW), which showed a significant association only with Braak NFT stages ≥I ($p = 0.050$).

Conclusion: These findings suggest that besides age, education, and genetic factors, other vascular risk factors were not associated with AD-related neuropathological changes and urge prompt actions be taken against cerebral small vessel diseases since evidence for effective prevention is still lacking.

Keywords: Alzheimer's disease, apolipoprotein E, atherosclerosis, cerebral small vessel diseases, neuropathology