Associations between cortical neurodegenerative pathology and white matter lesions

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Introduction: Cerebral white matter lesions (WML) encompass structural damage and loss of integrity of the cerebral white matter (WM) due to WM rarefaction (i.e., demyelination and axonal loss). WML frequently occur in brains of both the non-demented and demented elderly, especially Alzheimer’s disease (AD), and are visualized as white matter hyperintensities (WMH) on pre- and post-mortem T2-weighted magnetic resonance imaging (MRI). The pathogenesis of WMH is typically associated with small vessel disease (SVD) of the WM. However, the pathogenic mechanisms underlying the development of WM changes are not well understood and previous studies suggest a broader, multifactorial aetiology of WML including WM damage secondary to both SVD-related ischemia and cortical AD pathology, i.e., depositions of hyperphosphorylated tau (HPτ) and amyloid-beta (Aβ) in which axonal loss is the result of neuronal loss or calpain-mediated degradation of cytoskeletal proteins, activated by AD pathology-related axonal transport dysfunction. Currently neither imaging nor routine histological techniques allow differentiation between ischemic or neurodegenerative causes of WM changes. Here we investigated the influence of HPτ, Aβ, and SVD on WMH, as assessed on post-mortem T2-weighted MRI, in human post-mortem brains.

Methods: In 23 AD and 13 control post mortem brains, we quantitatively assessed cortical HPτ and Aβ burden in 24 cortical regions throughout the cortex by measuring the percentage area covered by AT8 immunoreactivity (HPτ-IR) and 4G8 immunoreactivity (Aβ-IR), respectively, and the severity of WM SVD by calculating SI of arteries/arterioles. Mean values of HPτ-IR, Aβ-IR, and SI in the frontal, temporal, parietal and occipital region, as well as a total value, were compared with age related white matter change scale (ARWMC) scores from post mortem MRI.

Results: HPτ-IR, Aβ-IR, and WM ARWMC scores were all significantly higher in AD cases compared to controls, while SI values were similar between groups. Partial correlations, controlled for age at death, revealed ARWMC scores correlated with HPτ-IR, Aβ-IR, and SI in various regions and the entire hemisphere. However, linear regression revealed that only HPτ-IR was a significant independent predictor of ARWMC scores in the frontal temporal and parietal regions and the entire hemisphere. When cases were limited to those with non/minimal (Braak NFT stage
Interpretation: We demonstrated that in various regions, as well as in the entire hemisphere, cortical HPτ burden predicted the severity of WMH independent of both cortical Aβ burden and WM SVD severity. However, in cases virtually lacking cortical HPτ pathology we found a strong correlation between SVD and WMH. These findings suggest that in general, both cortical HPτ pathology and WM SVD may lead to WMH; however, in AD, WMH are primarily associated with cortical HPτ pathology, while WM SVD may be only an additional contributing factor. On the other hand, in cases virtually lacking cortical HPτ pathology WM SVD seems to play an important role in the development of WMH. Further studies are warranted to better determine the underlying pathological processes that may lead to WMH.