APOE Genotype and White Matter Hyperintensities in Sporadic Alzheimer Disease

Letter to the Editor: Etiology of White Matter Hyperintensities in Autosomal Dominant and Sporadic Alzheimer Disease

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To The Editor:

We read with interest the paper entitled, "**Etiology of White Matter Hyperintensities (WMH) in Autosomal Dominant and Sporadic Alzheimer Disease (AD)".**[1] Using multimodal imaging data from three complimentary cohorts (DIAN, ADNI, and HABS), the authors concluded that the results strongly suggest cerebral amyloid angiopathy (CAA) as the likely etiology for WMH in AD.

We previously examined cross-sectional T1/T2-weighted MRI and neuropsychological data from patients with AD and dementia with Lewy bodies (DLB) from the Sunnybrook Dementia Study (SDS) and in an AD sample from ADNI.[2] Using a robust imaging pipeline to quantify WMH volume in SDS, we demonstrated that greater WMH burden was strongly associated with worse performance on multiple cognitive domains, including attention/executive functions, learning/ memory, and language, in *APOE-ε4* carriers. We did not observe such associations in non-carriers. Meta-analyses of results from SDS and ADNI (n=487) showed that the association between greater WMH burden and worse cognition was indeed only present in *APOE-ε4* carriers.[2] We hypothesized that since *APOE-ε4* is a genetic risk factor for CAA, AD and DLB, WMH in *APOE-ε4* carriers with AD, DLB or mixed AD with DLB may be more likely to be due to CAA and might be more 'toxic' to cognition than WMH caused by ischemia secondary to cardiovascular risk factors alone. This hypothesis was partially supported by examining a small autopsy subset of SDS (n=34): all patients (7/7) homozygous for *APOE-ε4* had CAA, compared to 39-50% of patients with other genotypes.

First, based on our findings, and the fact that *APOE-ε4* increases the risk of CAA,[3] we wonder if the authors looked at the effects of *APOE* genotype in their large imaging cohort, particularly in those with sporadic AD/mild cognitive impairment. Given the increased risk of both parenchymal and intravascular amyloid deposition posed by *APOE-ε4*, if *APOE-ε4* status is associated with WMH increase even in amyloid PET-negative individuals, this would support the idea that the relationship between brain amyloid and WMH is through the presence of CAA. Second, it would be helpful to know why the authors used only a measure of global atrophy, i.e., a non-specific marker of neurodegeneration, as opposed to more specific markers of AD-related neurodegeneration, such as hippocampal atrophy, focal medial temporal lobe loss or cortical thinning.[4,5] We believe that inclusion of *APOE* genotype and more specific AD-regional atrophy patterns might account for additional variance in their study.

References:

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