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White matter hyperintensities and Alzheimer's disease: An alternative view of an alternative hypothesis

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Abstract

White matter hyperintensities (WMH) - - areas of increased signal appearing on T2-weighted magnetic resonance imaging - - are associated with Alzheimer's disease (AD) risk and progression in late onset and genetic forms. Although typically attributable to macrostructural damage due to small vessel cerebrovascular disease or dysfunction, in a paper by Garnier-Crussard and colleagues[1], the authors review recent work suggesting an additional Wallerian-like component to WMH and argue that the elevated WMH seen in AD is a downstream phenomenon secondary to neurodegeneration. Here, we maintain that consideration of pathological correlates, animal work, brain perfusion patterns, longitudinal and incident data, and vascular risk factors provides evidence that is not inconsistent with a vasculogenic source of WMH. Future studies inspired by the consistent observations linking WMH to AD are needed to continue to understand potential vascular contributions to the disease.

We read with interest the recent article by Garnier-Crussard and colleagues[1], which hypothesized that white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) not only have a vascular origin *but also* are secondary to neurodegeneration that results from Alzheimer's disease (AD) pathology. We agree wholeheartedly with the authors' summary, but would like to push back, gently, on some of their conclusions, particularly those arguing that because WMH are often seen in the context of AD and not always associated with vascular risk factors, they do not reflect cerebrovascular changes. We highlight alternative interpretations that are more consistent with vasculogenic source of WMH even in the context of AD.

Central to the argument posed by Garnier-Crussard and colleagues is the observation that WMH and markers of white matter damage correlate with features of tau pathology

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Conflicts of interest

Dr. Brickman is a co-inventor of a US patent (US Patent US9867566B2) titled, "Technologies for white matter hyperintensity quantification." BR has nothing to disclose.

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and neurodegeneration at autopsy. While one interpretation could be that WMH reflect Wallerian-like degeneration, an equally feasible interpretation is that the vascular damage caused by subtle hypoperfusion or other vascular drivers of WMH *give rise* or *cause* tau pathology and neurodegeneration observed in AD[2]. We tested this idea experimentally in a murine model of WMH[3], in which aged wildtype mice receiving transient occlusion of the middle cerebral artery (tMCAo) had white matter abnormalities relative to sham controls, mirroring the macrostructural damage we suspect underlies WMH. The tMCAo mice had increased biofluidic tau concentrations and hyperphosphorylated tau pathology in the ipsilateral hippocampus and cerebral hemisphere, consistent with previous work showing evidence of hypoperfusion injury in hypertensive rats that induce sporadic hyperphosphorylated tau and neuronal death[4]. We can infer from human pathology studies that there is a relationship among WMH, tau pathology, and neurodegeneration, but we cannot determine causality from these data.

Investigators interested in this topic are familiar with the stereotypical anatomical pattern of WMH progression. White matter hyperintensities typically appear first in periventricular regions and then expand towards cortex. The white matter regions directly abutting cortex, reflecting cortical-cortical projections, are typically spared in AD. This WMH distribution more closely aligns with the brain's perfusion patterns and the vulnerability of watershed regions to changes in blood supply and small vessel injury. If WMH in AD are due to Wallerian-like degeneration, we would expect white matter regions proximal to observed grey matter atrophy to be affected most prominently, reflecting axonal "die back" from the primary neuronal injury; however, this pattern is almost the exact opposite of what is typically observed. The anatomical colocalization among atrophy patterns, pathological changes, metabolic dysfunction, and WMH could be explained by an upstream deficit in regional perfusion.

There is appeal in interpreting findings related to AD in the context of the amyloid-tau-neurodegeneration ('ATN') cascade that is in the current Zeitgeist. Garnier-Crussard and colleagues argue that WMH in AD are the result of neurodegeneration, a late-stage phenomenon in the ATN framework. However, the data do not support this temporality. Regional WMH precede incident clinical AD diagnosis[5] and are elevated over twenty years prior to expected symptom onset in autosomal dominant AD[6]. Higher WMH volumes predict faster entorhinal cortex atrophy and increasing tau biomarker concentrations, but not vice versa[7] and elevated posterior WMH predict longitudinal cortical atrophy in AD-related areas[8]. Taken together elevation in regional WMH is a phenomenon that occurs earlier than expected neurodegeneration in AD and predict *subsequent* clinical symptoms and neurodegeneration. These studies are more consistent with a conceptualization of WMH as a causal driver rather than the result of AD-related neurodegeneration.

Our last point addresses the observation that WMH and AD appear to be linked even in populations with minimal vascular risk factors[6, 9]. Garnier-Crussard and colleagues note that WMH in AD do not reflect cerebrovascular disease because they cannot be attributable solely to vascular risk factors. Our view is that there is likely an "endogenous" or genetic cerebrovascular component to AD that can certainly be potentiated by exposure

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to vascular risk factors, but that vascular risk factors may not be necessary for there to be a vascular component to AD pathogenesis. Considering evidence of neuroinflammatory and vascular deficits at the level of endothelium/neurovascular unit in AD[10], there are likely important pathways that still need to be uncovered that link WMH to AD apart from vascular risk factors. We conclude that we should think outside of the ATN Zeitgeist and rather than dismissing one of the most consistent neuroimaging observations in AD research as simply secondary to downstream neurodegeneration, we have an opportunity to design more sophisticated experiments inspired by WMH to understand potential vascular contributions to AD more fully.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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