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Contribution of Cerebrovascular Health to the Diagnosis of Alzheimer Disease

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Sporadic alzheimer disease (ad) is a multifaceted neurodegenerative syndrome with complicated and unclear etiology that results in debilitating cognitive decline in old age. Although several decades of AD research resulted in major scientific advancements in identifying and tracking the disease, as well as discovering many salient genetic and environmental factors, considerably less progress in the development of efficacious therapies has been made. A major challenge for the field has been identifying sensitive and specific markers for detection in early stages of the disease, because by the time clinical symptoms are present, neuropathology is already quite advanced.[1] Understanding the cascade of events that is unique to AD is complicated by the fact that

AD exhibits a diverse clinical presentation and is often concomitant with other types of brain injury and dementia. A common example of this comorbidity is vascular disease, which can act as a risk factor for AD[2] but also contributes to cognitive decline in its own right.[3] Understanding the nature of the contributions of vascular pathology to AD is an important (and open) area of current research. Knowing if cerebrovascular disease plays an early and initiating role in the formation of AD neuropathology may have a significant impact on strategies to treat or even prevent the disease since vascular diseases are often highly responsive to treatment. However, cerebrovascular disease may simply occur in parallel to the development of AD pathology as a correlate and by-product of the aging process. Research examining the impact of various vascular health risk factors and specific neurovascular changes that can be measured in the human brain in vivo, along with biomarkers for AD (eg, β-amyloid [Aβ] positron emission tomography imaging of aggregated fibrillar amyloid plaque), are needed to elucidate this question.

Toward this aim, in their article in this issue of *JAMA Neurology*, Provenzano and colleagues[4] used data from the Alzheimer's Disease Neuroimaging Initiative cohort to examine the impact of small vessel cerebrovascular disease and Aβ pathology on the clinical expression of AD. Specifically, they investigated whether positron emission tomography–measured Aβ deposition and leukoaraiosis (ie, white matter hyperintensity [WMH] burden) predicted AD status. Second, they aimed to determine whether WMH volume discriminated between individuals with and without a clinical diagnosis of AD among individuals who showed Aβpositivity. Third, they examined whether WMH in addition to Aβ status could be used to predict conversion from mild cognitive impairment (MCI) to AD over a mean longitudinal period of 2.5 years.

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Provenzano and colleagues found that a high Aβ level and increased WHM burden independently predicted AD diagnosis among all Aβ-positive individuals. Those individuals who carried an AD diagnosis had greater WMH burden than the normal controls who also showed elevation in Aβ level. Finally, Provenzano and colleagues classified a group of individuals with MCI into 4 categories by WMH and amyloid load: low on both amyloid and WMH, high on WMH only, high on amyloid only, or high in both factors. They found a monotonic increase across these risk groups, respectively, where the group with elevations in both WMH and Aβ evidenced the highest conversion rate from MCI to AD.

These results indicate that among individuals with an elevated Aβ level, WMH burden can discriminate between clinical AD and cognitively normal groups. Additionally, both amyloid and WMH status combined to best predict who would convert to AD among those with MCI. As Provenzano and colleagues point out, knowledge of an individual's WMH burden appears to add predictively to clinical outcome beyond amyloid status. This study adds to a significant and growing body of evidence that suggests that vascular disease may not always be a completely distinct pathologic entity because it is often found concomitantly in the brains of individuals who convert to AD. Provenzano and colleagues highlight the fact that the Alzheimer's Disease Neuroimag-ing Initiative participants are screened against severe forms of cerebrovascular disease, and even in those individuals with relatively good vascular health, WMH still contributed to the predictive power of AD conversion beyond Aβ status. The relatively mild representation of vascular risk in the study sample calls into question the pathological processes that might underlie the development of WMH. Rather than reflecting small vessel disease exclusively, Provenzano and colleagues suggest that WMH may result from proinflammatory processes in the brains of older adults. Indeed, the pathophysiology of leu-koaraiosis is poorly understood and in need of further study. Nevertheless, this study suggests that information about a patient's white matter health may aid in identifying those most at risk for conversion to AD. These findings have important clinical implications in light of the observation that 20% to 30% of cognitive healthy older adults show elevated amyloid levels.[5,6]

Although the Provenzano et al study could be interpreted as evidence that small vessel cerebrovascular disease (to the extent that WMHs reflect it) contributes directly to the development of AD, the specificity of the findings to AD pathophysiology is not clear. It is possible that the results reflect individual differences in the threshold for detection of AD. That is, that the effects of additional neural hits beyond Aβ accumulation compromise the brain's ability to maintain cognitive function at a given level. Thus, WMH burden may be but one additional consequence of brain aging that may or may not contribute directly to the pathogenesis of the disease. Given the diversity of individual differences in the expression of AD (and consequently the differing time course of its clinical detection), individuals with the additional burden of compromised white matter integrity may show cognitive symptoms in the clinical range sooner than those without WMH who may be able to ward off the effects of the neural changes on cognition for a longer period. In fact, in a longitudinal study of normally aging individuals, 5-year progression of WMH was most strongly associated with cognition in those individuals with vascular risk factors.[7] A fruitful next step would be to test this hypothesis by strategically examining the predictive power of other aging-related brain changes in addition to WMH, such as atrophy, mineralization, mi-crobleeds, and genetic risk factors in the context of elevated Aβ level, to determine the specificity or additive effects of various neural changes in predicting pathology with aging.

The possibility that WMHs are directly related to the accumulation of Aβ is not well studied, although a recent study[8] reported no association between WMH load and cerebrospinal Aβ42, an amyloid-specific marker for AD that reportedly decreases early in the course of AD, reflecting impaired amyloid clearance. In vivo estimates of Aβ were not reported in that

study for direct comparison. However, another recent study in healthy older adults with amyloid burden reported no reliable association between WMH and positron emission tomography–derived estimates of amyloid deposition.[9] Although these reports are not definitive and are in need of replication, they suggest that WMH and neural markers of Aβ pathology may not be directly related, although WMHs do contribute to predicting who might develop AD, when amyloid load is known.

None of these findings directly refute the possibility that vascular factors play a critical role in the development of AD, at least for some individuals. Epidemiologi-cal studies have shown that many cardiovascular risk factors such as midlife hypertension, diabetes mellitus, hypercholesterolemia, metabolic syndrome, and smoking can increase the risk of AD in later life. Recently, we reported evidence of an association between hypertension and cerebral amyloid deposition.[10] In cognitively normal middle-aged and older adults, hypertension diagnosis was associated with elevated amyloid in individuals with genetic risk for AD (*APOE* e4 carriers), and increases in pulse pressure predicted elevated amyloid burden beyond the effects of age. There is also evidence that intervention studies that improve vascular function may attenuate AD pathology.[2] Of course, understanding the relationship of vascular disease to amyloidosis is only part of the story. Additional research is needed to test the relationship of vascular pathology to tau hyperphosphory-lation and tangle formation, which is hypothesized to be a necessary cofactor with Aβ in the expression of AD.

Whether the contribution of vascular health to AD is entirely independent of its basic neuropathology (amy-loid deposition and tauopathy), merely concomitant with it, or sometimes a trigger for its expression, the presence of vascular risk exacerbates cognitive aging and better and earlier control of its manifestations (eg, hypertension, diabetes) will make a positive contribution to public health, both cardiovascular and cognitive. Longitudinal studies that carefully track vascular health risk factors and measure the development of key biomarkers for AD within individuals over time are essential to understanding the nature of the interaction between vascular disease and cognitive aging and the conversion from MCI to AD diagnosis.

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