Dipping to clear amyloid

Cerebrovascular reactivity and neurodegeneration—cause or effect?

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In this issue of *Neurology*®, Tarumi et al.[1] report an interesting study on a small sample of 40 persons with amnestic mild cognitive impairment (MCI) who were free of major vascular disease, sleep disorders, uncontrolled hypertension, and diabetes. They found that 2 indicators of a healthy, reactive vasculature, a greater reduction in systolic blood pressure (BP) when asleep (compared to the BP when awake), and greater cerebrovascular reactivity in response to physical activity, assessed using transcranial Doppler insonation of the intracranial middle cerebral artery, were each associated with lower PET amyloid burden in the posterior cingulate gyrus, a finding believed to be an early marker of Alzheimer disease pathology.

Circadian rhythms in BP appear to allow for higher BPs and greater perfusion of the awake, metabolically more active brain, while reducing chronic stress on the cerebral vasculature through lower BPs at night, when cerebral metabolic rates go down. The absence of such nocturnal dipping (<10% fall in BP) has been associated with a greater prevalence of vascular and metabolic risk factors, higher mortality, a higher prevalence of cardiovascular events including stroke,[2] greater prevalence of MRI markers of cerebral small vessel disease (white matter hyperintensities and lacunar infarcts),[3] and worse performance on cognitive function tests.[4] A nondipping status appears to be one early marker of vascular stress or injury and has been associated with other functional markers, including carotid femoral pulse wave velocity and cerebrovascular reactivity.[5,6] Indeed, ambulatory 24-hour BP recording has been described as the gold standard for assessing vascular risk; however, it is expensive, somewhat burdensome, and its incremental utility over an office BP in primary and secondary prevention of cardiovascular events remains uncertain.[7] Prior studies relating ambulatory BP to subclinical brain injury were largely restricted to cognitively normal persons with or without other evidence of vascular disease. The current study is the first to specifically target persons with MCI and the first to assess PET amyloid burden, a marker of neurodegeneration, rather than a conventional marker of vascular brain injury.

The ability of the cerebral vasculature to respond to stimuli (reactivity) is another sign of vascular health, this time more specific to the cerebral vasculature. Cerebrovascular reactivity has been assessed as a response to the vasodilatory effect of inhaled carbon dioxide or breath-holding; in the past year, lower cerebrovascular reactivity has been observed in persons with Alzheimer disease compared to healthy persons, and postulated to predict conversion from MCI to dementia.[8] However, a more physiologically relevant stimulus to study cerebrovascular reactivity is the change in systemic BP and heart rate that accompanies physical activity.

This cross-sectional study does not allow any inference regarding causality. Two possible explanations for the observed associations discussed by the authors are that decreased vascular reactivity might increase parenchymal amyloid deposition, or that both result from underlying age-related or pathologic processes. Injury to the microvasculature may be one pathway mediating the association of impaired cerebrovascular reactivity with increased parenchymal amyloid deposition. Sleep disturbances may be another confounder as poor sleep has been linked to impaired glymphatic clearance,[9] and undiagnosed obstructive sleep apnea (the authors did exclude persons previously known to have sleep apnea) has been associated with both a nondipping status and increased brain amyloid.[10,11]

These intriguing findings, directly linking vascular reactivity and neurodegeneration, need to be replicated in larger samples, but if validated they expand our understanding of vascular contributions to Alzheimer disease and suggest new therapeutic options to reduce the risk of progression from MCI to clinical dementia.

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DISCLOSURE

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