Does Increased Arterial Stiffness Herald Cognitive Impairment?

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See related article, p 2256.

Cognitive impairment or dementia is one of the most frequent causes of disability in the elderly. A recent meta-analysis reports global prevalence of dementia from all causes to be between 5% and 7% of adults of age >60 years. It doubles every 5 years and reaches >30% at the age of 90 years in the most regions of world. Dementia has become a significant economic burden in aging societies worldwide. There is a transitional phase between normal function and dementia. The term mild cognitive impairment (MCI) has been introduced to define such transitional cognitive dysfunction in the clinical and research settings. The prevalence of MCI is close to 20% in people aged >70 years. Given the fact that elderly patients with MCI have a high risk of developing dementia, identification of early biomarkers of MCI would be a critical step to facilitate construction of measures for prevention of dementia.

Arterial stiffness refers to a reduction in the ability of large arteries to readily accommodate the increase in blood volume ejected from the heart during systole. It has been proposed as an indirect measure of brain microcirculation and small-vessel damage. Recent evidence has suggested that cerebral small-vessel disease is involved in pathophysiology of cognitive decline, vascular dementia, and Alzheimer disease. Therefore, arterial stiffness may be a novel imaging biomarker of MCI and dementia.

In this issue of Stroke, Pase et al6 report a strong association between aortic stiffness, measured by pulse wave velocity, and the development of MCI and incident dementia >10 years of surveillance in a sample of 1101 dementia-free Framingham Offspring Study participants. Higher aortic stiffness was associated with an increased risk of MCI (hazard ratio, 1.40; 95% confidence interval, 1.13–1.73), independent of age, education, APOE 4 status, vascular risk factors, and cardiovascular diseases. Similarly, higher aortic stiffness was associated with an increased risk of dementia (hazard ratio 1.45; 95% confidence interval, 1.13–1.87), independent of age, education, and APOE 4 status, but not independent of vascular risk factors. The authors reported that among individuals without diabetes mellitus, the higher aortic stiffness was associated with an increased risk of incident all-cause dementia (hazard ratio 2.27; 95% confidence interval, 1.28–4.05). This association was not present among individuals with diabetes mellitus. Interestingly, central pulse pressure and prevalent hypertension were not associated with increased risks of MCI, all-cause dementia, or Alzheimer disease.

Although a wealth of evidence in cross-sectional studies shows that increased arterial stiffness is associated with poor cognition, data from longitudinal studies are sparse. Several studies have reported an association between the top tertile of pulse wave velocity and greater annual decline in Mini Mental State Examination and specific cognitive domains such as executive function, processing speed, or verbal memory. Studies on the long-term temporal relationships between arterial stiffness and MCI are limited and therefore the article by Pase et al contributes considerably to filling the knowledge gaps linking a long-term effect of arterial stiffness to increased risk of MCI. The study provides compelling evidence for an important vascular role in the pathogenesis of MCI. Vascular risk factors including hypertension, diabetes mellitus, and adiposity are contributing factors to MCI and dementia. However, Pase et al show that the effect of aortic stiffness on all-cause dementia is stronger among those without diabetes mellitus, indicating that an association between diabetes mellitus and dementia may not be mediated by vascular changes but rather through metabolic mechanisms. Whether arterial stiffness can be a predictor or biomarker of MCI and dementia independent of vascular and metabolic risk factors deserves further investigation.

The finding of arterial stiffness associated with incident dementia is congruent with some previous results. A large body of evidence has suggested a link between vascular factors and dementia including Alzheimer disease. Ischemic brain injury manifested as small-vessel disease is commonly seen in patients with dementia. Although arterial stiffness has been associated with aging, vascular risk factors, cardiovascular diseases, genetic disorders, and autoimmune diseases, the role of arterial stiffness in MCI and dementia is unclear. The mechanism by which arterial stiffness may affect cognition is, however, plausible. Because the brain microcirculation has low impedance or resistance, small cerebral arteries are more vulnerable to greater blood flow pulsatility transmission in the setting of increased systemic arterial stiffness. Elevated pulsatility combined with increased flow volume may lead to endothelial dysfunction and microvascular brain damage. Indeed, arterial stiffness has been related to brain small-vessel pathology such as white matter lesions, lacunar infarcts, and microbleeds, as well as to medial temporal lobe atrophy in the elderly with memory disorders. Therefore, this study emphasizes the potential contributing role of arterial stiffness to cognitive dysfunction and to overall cognitive health.
It is important to note several limitations to this study. First, as often the case in observational longitudinal studies, the causality between arterial stiffness and MCI or dementia cannot be determined. Although the study is based on the well-characterized population sampled from the reputable Framingham Heart Study, these results may not be generalizable to other populations, especially to race-ethnic diverse populations. These results, therefore, need to be confirmed in other samples. Arterial stiffness can cause brain injury through silent brain infarcts and white matter damage; however, there is no direct evidence of brain injury variables analyzed in this study. And finally, structural brain damage leading to cognitive impairment may be predominately affected by stiffness in brain arteries or in direct brain-supplying arteries rather than by systemic arterial stiffness. Although peripheral pulse wave velocity is considered a gold standard for measuring arterial stiffness, it assumes that stiffness is equally distributed across the arterial tree. However, in the case of regional brain damage, this may not be an appropriate assumption, and therefore local stiffness measured in intracranial arteries may be a better marker of brain structural changes and cognitive decline.

Nevertheless, the finding of an association of arterial stiffness with an increased risk of MCI and incident dementia opens new horizons for the investigation of vascular mechanisms of dementia and the search for a valid and early vascular biomarker for MCI and dementia. Interventions that modify vascular risk factors and arterial stiffness have enormous potential for prevention of cognitive impairment and dementia.

Disclosures

None.

References


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