Midlife Blood Pressure, Amyloid-β, and Risk for Alzheimer Disease
One More Reason to Treat Hypertension

Merrill F. Elias, Adam Davey

The association between hypertension and vascular dementia (VaD) is well established and biologically plausible. Hypertension and small vessel disease are common in vascular cognitive impairment.1 The relatively more recent discovery that hypertension is associated with increased risk of Alzheimer disease (AD) is less intuitively understandable, and so the search for mechanisms continues. Recognizing that sensitivity may be preferred to specificity in the early stages of seeking to identify plausible mechanisms, the report by Shah et al2 in this issue of Hypertension takes an important step in this direction. Using a prospective design, these investigators examined the association between midlife blood pressure (BP) and amyloid-β (Aβ) peptide levels and risk for late-life AD and VaD in 667 Japanese-American men participating in the Honolulu Asia Aging Study.

Data for the analyses were taken from 7 examinations, =3 years apart beginning between 1965 and 1967 and ending in 2000. The outcome measures were prevalent and incident AD (with and without contributing cardiovascular disease), pure AD (n=38), and VaD (n=24). Cerebral amyloid angiopathy (CAA), Aβ neuritic plaques, and neurofibrillary tangles were evaluated postmortem in a subsample of 73 men.

Midlife BP was not associated with prevalence or incidence of VaD. However, for the all-AD outcome category there was an interaction between diastolic BP and plasma Aβ measures for prevalent AD. Estimated risk for late-life dementia for every 1-SD decrease in plasma Aβ at midlife was higher for diastolic hypertensive individuals (BP >90 mmHg) than for persons with low diastolic BP (≤80 mmHg) for both Aβ1–40 and Aβ1–42 assays. For the smaller pure AD group this same result was obtained when the Aβ1–40 but not when the Aβ1–42 assay was used, although the trend was in the same direction for both assays. This finding is biologically plausible. As Shah et al2 make clear in the rationale for their study, Aβ peptides are neurotoxic and promote vasodestruction and cerebral vascular pathology, and when lower values of Aβ are seen in plasma, higher levels are seen in cerebral cortical tissue attributed either to increased production or decreased clearance of Aβ.

Shah et al2 conclude that plasma Aβ levels begin declining ≥15 years before AD is diagnosed and that the association of Aβ to AD is modulated by midlife BP. They hypothesized that “elevated BP may compromise vascular integrity leading to cerebral amyloid angiopathy and impaired Aβ clearance from the brain” (p 780). We will use the term “effect modification” to describe the role of BP.

Modification of the relation between Aβ and incident AD was only observed for diastolic BP. Shah et al2 speculate that the absence of an interaction of Aβ and BP for systolic BP may be related to emphasis on lowering diastolic BP during the BP surveillance period or to treatment protocols in place during this same period. This explanation strikes us as somewhat unlikely for several reasons. Systolic BP earlier in life has been a predictor of cognitive performance and dementia later in life in studies by this group using this same prospective design and study population.3,4 For example, in a study with dementia as the outcome, both systolic and diastolic BPs at midlife were related to dementia later in life, and this phenomenon was seen only in the 57% of the sample that was untreated at midlife.4 In the Framingham cohort, for whom hypertensive individuals were untreated between 1950 and 1954, both higher systolic and diastolic BPs predicted modestly lower cognitive performance 12 to 14 years later.5 Thus, in our view, other explanations for the absence of effect modification by systolic BP need to be considered.

One possible explanation may lie with the especially destructive influence of exposure to Aβ peptides on small vessels and the influence of small vessels on diastolic BP. Aβ peptides promote vasocostriction6,7 and, when deposited in microvessels, facilitate vascular pathology and dysfunction.1,6,7 Chronic vasocostriction in the small arteries, arterioles, capillaries, and veins plays an important role in diastolic hypertension. Moreover, CAA is a common form of small vessel disease.1 In CAA, deposition of Aβ in the vascular media and adventitia leads to loss of integrity of the vessel wall,1,6,7 with consequent large and small brain hemorrhage, and CAA is well recognized as a risk factor for brain ischemia and cognitive impairment independent of stroke.5,7 In ischemic lesions seen in small vessel disease, the lumen of the vessel is restricted, leading to a state of chronic hyperfusion of the white matter and consequent degeneration of myelinated fibers.1

Measurement of plasma Aβ once at a single occasion separate from BP assessment is a study limitation noted by

From the Department of Psychology and Graduate School of Biomedical Sciences (M.F.E.), University of Maine, Orono, ME; Department of Public Health (A.D.), Temple University, Philadelphia, PA.

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Correspondence to Merrill F. Elias, Department of Psychology, 5742 Little Hall, University of Maine, Orono, ME 04469-5742. E-mail mfeliasumaine@aol.com

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Shah et al,2 and their suggestion for in vivo analysis of brain-specific burden using positron emission tomography is well taken. In addition, to explore the possibility that chronic exposure to Aβ and hypertension explains the role of BP in AD, future studies will need to obtain multiple in vivo measures of Aβ, systolic BP, and diastolic BP at multiple points in time before diagnosis of Aβ and VaD. The amount of exposure over time to both Aβ and hypertension should be associated with the subsequent risk of dementia. In the study by Shah et al,2 low plasma Aβ was associated with CAA, but this was not true for neuritic plaques and neurofibrillary tangles. Possibly these changes would be seen in further work with longer exposure to Aβ. Longitudinal studies beginning at midlife or earlier can address these issues and others, such as why systolic BP and pulse pressure did not modify relations between Aβ and AD in the study by Shah et al.2 It is possible that systolic BP and pulse pressure may become more important modifiers of relations between Aβ and AD at some point between midlife and later life where atherosclerosis appears to play an increasingly important role in decline in cognitive performance.8,9

Future studies aside, the Shah et al2 article provides provocative evidence that midlife hypertension modifies (enhances) the association between Aβ and AD. We feel it important to examine the extent to which diastolic versus systolic BP mediates the relation between Aβ and cognition. Path analysis is a particularly useful statistical method for examining the extent to which an intervening variable mediates relations between a predictor and an outcome (ie, mechanisms and potentially causal pathways). In the Figure, we display a simple path model that can be elaborated on, as required by specific hypotheses, including revised hypotheses based on data in other ethnic groups and with larger samples challenging the exclusive role of diastolic BP in Aβ effect modification and mediation.

Regardless of future outcomes with respect to diastolic versus systolic BP, the Shah et al2 findings have important and obvious implications for treatment strategies with respect to preserving cognitive functioning. According to the amyloid hypotheses, various stages of Aβ aggregation disrupt brain cells by disrupting cell-to-cell communication, activating immune cells that trigger inflammation, destroying disabled cells, and ultimately killing them.10 The Alzheimer’s Association10 describes work in animals with experimental drugs that would decrease the production, prevent the aggregation, or increase the removal of Aβ from the brain, but these treatments are not currently available. Until then, we have yet another reason to prevent, detect, and treat hypertension as early as possible in the life cycle.

Disclosures

None.

References

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