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. 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 al 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 al make clear in the rationale for their study, Aβ peptides are neurotoxic and promote vasostenosis 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 al 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.

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 vasoconstriction and interneuronal and cerebral vascular pathology, and when lower values of Aβ are seen in plasma, higher

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.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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

Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.111.189464

Merrill F. Elias, Adam Davey

See related article, pp 780–786

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

Hypertension is well established and biologically plausible. Hypertension and small vessel disease are common in vascular cognitive impairment. 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 al 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 al make clear in the rationale for their study, Aβ peptides are neurotoxic and promote vasostenosis 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 al 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.

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 vasoconstriction and interneuronal 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 al 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.

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 vasoconstriction and, when deposited in microvessels, facilitate vascular pathology and dysfunction. Chronic vasoconstriction 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. In CAA, deposition of Aβ in the vascular media and adventitia leads to loss of integrity of the vessel wall, 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. In ischemic lesions seen in small vessel disease, the lumen of the vessel is restricted, leading to a state of chronic hypoperfusion of the white matter and consequent degeneration of myelinated fibers.

Measurement of plasma Aβ once at a single occasion separate from BP assessment is a study limitation noted by
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 al 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. The Alzheimer’s Association 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

Midlife Blood Pressure, Amyloid-β, and Risk for Alzheimer Disease: One More Reason to Treat Hypertension
Merrill F. Elias and Adam Davey

Hypertension. 2012;59:771-772; originally published online March 5, 2012;
doi: 10.1161/HYPERTENSIONAHA.111.189464
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/59/4/771

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/