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Preventing Dementia by Treating Hypertension and Preventing Stroke

J. David Spence

In this issue of *Hypertension*, Korf et al¹ report from the Honolulu Asia Aging Study that untreated hypertension was significantly associated with hippocampal atrophy. They had previously shown that untreated hypertension was associated with midlife cognitive decline² and with Alzheimer disease and vascular dementia.³

This new finding strengthens the value of hippocampal atrophy as an early predictor of cognitive decline. It also adds importantly to a growing body of evidence that hypertension and stroke beget dementia and that treatment of hypertension, as well as prevention of stroke, prevents dementia. In the past this might have been explained by a reduction of vascular dementia, but it is apparent that the lines between vascular dementia and Alzheimer disease are becoming blurred.

Hypertension is strongly associated with the subsequent development of dementia. In Linxiang County, China, high blood pressure was shown in multiple logistic regression to be a risk factor for Alzheimer disease (OR 1.97), with a significant dose–response relationship.⁴ Skoog et al⁵ found that subjects who developed dementia at 79 to 85 years of age had significantly higher blood pressures 15 years earlier. It seems likely that the relationship between hypertension and dementia is via stroke, because stroke is also associated with increased risk of dementia.

In the Framingham study, stroke doubled the incidence of dementia, and the hazard ratio was even greater at 2.6 for younger subjects.⁶ In North Manhattan, the relative risk for Alzheimer disease was 1.6 for those with stroke, and this increased with addition of vascular risk factors, including hypertension (RR 2.3) and diabetes (RR 4.6).⁷ Snowdon et al showed in the Nun study⁸ that even 1 or 2 small lacunar infarctions at the base of the brain markedly increased the likelihood that Alzheimer disease was expressed as dementia. Soon after that, Forette et al⁹ showed that treating isolated systolic hypertension reduced Alzheimer dementia by half.

Apart from hypertension, other vascular risk factors appear to be associated with increased risk of dementia, including diabetes^{7,10,11} and elevated total homocysteine.^{12,13} Indirect results suggest that the use of statin drugs seems to reduce the

risk of dementia¹⁴ and stroke¹⁵; these hypotheses will be tested directly in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial.¹⁶

It remains to be seen whether blood pressure control per se will achieve all the benefit of treatment or if treatment with particular types of antihypertensive therapy may confer additional benefits. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study¹⁷ losartan was more efficacious in reducing stroke compared with atenolol, despite virtually identical blood pressure control. Treatment with angiotensin-converting enzyme inhibitors (ACEi) reduced decline in cognitive function in both the PROGRESS trial¹⁸ (in which diuretic was combined with ACEi in most cases) and the Heart Outcomes Prevention Evaluation (HOPE) trial.¹⁹ In the Study on COgnition and Prognosis in the Elderly (SCOPE) trial,²⁰ candesartan reduced decline of cognitive function among elderly hypertensive patients with early decline at the beginning of the trial (with a minimal score ≤ 28). It should be noted that there are concerns regarding the SCOPE results, which were weakened by conversion of the study from a placebo-controlled trial (after publication of new guidelines that made it unethical to continue with a placebo-controlled study) to a trial of candesartan versus usual care, thus substantially reducing power. Valsartan, an angiotensin receptor antagonist, was recently shown to be associated with less cognitive decline than enalapril, suggesting that angiotensin receptor blockade may have particular advantages.²¹

It is particularly interesting that in the Honolulu study, diastolic hypertension was more strongly associated with hippocampal atrophy than was systolic hypertension. This suggests that small vessel hypertensive disease, as opposed to atherosclerosis, may be involved in hippocampal atrophy, or with thalamic lacunar infarctions that can cause dementia²² and that control of hypertension, which virtually eliminates lacunar infarctions,²³ may be more important in preventing dementia than other modalities that reduce stroke.

Withholding antihypertensive therapy does no favor to the elderly.

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