Further Evidence for Vascular Mediation of Alzheimer's Dementia Pathogenesis?

John C.S. Breitner

The conundrum of Alzheimer's dementia (AD) and cerebrovasculopathy was summed up admirably 34 years ago: "Our ignorance far exceeds our knowledge about cerebral blood flow in dementia"(1). Since that time, we have learned that "pure" vascular dementia is relatively rare (2), but the admixture of AD pathology with vascular lesions (3) or alteration in tissue composition of white matter (4) is common. We have also learned of complex associations between hypertension and AD pathogenesis, with most evidence suggesting that hypertension in middle life or early senescence is a stronger predictor of subsequent dementia than is high blood pressure at the time when risk of AD is greatest (5). It remains controversial whether midlife blood pressure is the "true" predictor of AD or whether disease processes that provoke dementia simultaneously induce a decline in arterial pressure. There is limited empirical evidence to support the former (6), but the matter is far from resolved.

When faced with such a mixture of observational evidence, we often look for answers in randomized controlled trials. Carefully conducted trials rely on randomization, masking, and other quality control measures to provide unbiased evidence that can be acquired in no other way. Such trials have their limitations, however: strictly interpreted, they test their hypothesis only under the conditions that characterize the experiment. In the instance of antihypertensive treatments and risk of dementia, trials are limited by the fact that they can examine effects of interventions only when these are administered in the years concurrent with (or preceding only slightly) the time that dementia onsets are observed. There are no hard and fast rules to tell us how far we can generalize from trial results to encompass other circumstances that are similar but not identical (7). As the authors of the present report note, clinical trial results are mixed on the question of antihypertensive treatments as a modifier of dementia incidence.

An important clue to the importance of vasculopathy (and, by implication, hypertension) in the pathogenesis of AD may be found in results from the Seattle-based Adult Changes in Thought study (8). This study's investigators systematically examined autopsies from a sequence of 211 decedents (20% of all those who died within a given interval) in a representative population sample. Because all of these individuals had been carefully evaluated clinically (usually over several years), one could contrast autopsy findings among 75 who died with neurodegenerative dementia versus 89 who were dementia-free at their last biennial evaluation. Pathologic characterization included the Consortium to Establish A Registry for Alzheimer's Disease plaque score, Braak staging of neurofibrillary pathology, cerebral microinfarcts, cortical Lewy bodies, cystic infarcts, and amyloid angiopathy. The analysis used a weighted multivariate logistic model to impute the strength of association between these pathological features and the presence of clinical dementia before death, thus reversing the time-honored approach of "verifying" a dementia diagnosis pathologically. The findings suggested that the pathologic features most closely associated with dementia included cortical microinfarcts (odds ratio [OR] for 2 or more such infarcts = 4.80). These microinfarcts were exceeded as predictors of dementia only by a Braak neurofibrillary score of V or VI (OR = 5.89) and neocortical Lewy bodies (OR = 5.08). Surprisingly, microinfarcts were stronger predictors of dementia than Consortium to Establish A Registry for Alzheimer's Disease (CERAD) plaque score (OR for "frequent" plaques = 1.31), cystic infarcts (OR for $\geq 2 = 2.37$), or amyloid angiopathy (for "moderate" or "severe," OR = 1.15).

These last results suggest that microvascular infarcts may be the Rodney Dangerfield of dementia neuropathology. Notwithstanding the Seattle group's results, these lesions have until now received practically "no respect."

This issue's article by Schneider *et al.* (9) may help to remedy this oversight and to promote an improved measure of respect by showing the importance of atrial natriuretic peptide as a predictor of progression ("conversion") from mild cognitive dysfunction to AD. Furthermore, this study suggests that the benefit of antihypertensive therapy in preventing such progression is limited to those with elevated levels of the peptide. Importantly, the beneficial effect in this subgroup seems most apparent in those who were relatively younger. The fact that these investigators could demonstrate these sorts of interactions (effect × peptide level, and effect × peptide level × age) in a sample of this size suggests that these relationships are strong. Information of this kind should help us disentangle the maze of both observational and trial evidence on the relationship of hypertension and vasculopathy with dementia. If these new results can be readily reproduced, they should open new avenues of exploration into both the causes of dementia and possible routes to its prevention.

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From the Centre for Studies on Prevention of Alzheimer's Disease, Douglas Mental Health University Institute, and the McGill University Faculty of Medicine, Montreal, Quebec, Canada.

Address correspondence to John C.S. Breitner, M.D., M.P.H., Centre for Studies on Prevention of Alzheimer's Disease, Douglas Mental Health University Institute, Perry E-2212, 6875 Blvd LaSalle, Montreal, QC H4H 1R3 Canada; E-mail: john.breitner@mcgill.ca.

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