Cognitive Impairment and Blood Pressure
Quo Usque Tandem Abutere Patientia Nostra?

Jan A. Staessen, Willem H. Birkenhager

That hypertension causes vascular dementia is long-established, but that blood pressure behaves as a continuous risk factor for Alzheimer disease continues to bewilder medical experts. The confusion stems from the lengthy latency period between the initiation of the disease and the appearance of symptoms. Moreover, in patients with Alzheimer disease, synaptic disconnection of the autonomic brain nuclei and physical immobilization often lead to a paradoxical fall in blood pressure. Cross-sectional studies, therefore, cannot disclose the true nature of the relation between dementia and blood pressure. Longitudinal studies generated the evidence that hypertension is a harbinger of cognitive impairment. In stroke-free Framingham participants aged 55 to 88 years and followed-up for >20 years, the composite score and measures of attention and memory were independently and inversely correlated with blood pressure at enrollment. Swedish studies of middle-aged men and septuagenarians, followed-up for 15 to 20 years, confirmed the relation between cognitive impairment and blood pressure. This association was tighter in subjects untreated for hypertension than in those treated. Compared with nondemented controls, blood pressure at follow-up remained elevated in patients with vascular dementia but decreased in patients with Alzheimer disease.

The incidence of dementia exponentially rises with age with rates of 5 to 10 cases per 1000 person-years at 70 years up to 20 to 40 cases per 1000 person-years at 80 years. With the exception of rare early-onset familial dementia, the medical profession usually views cognitive decline as a problem of the elderly. Here, the work of Elias et al breaks new ground. They kept the participants of the Main–Syracuse Longitudinal Study of Hypertension in follow-up for 20 years. They used a sophisticated 2-step growth curve method to model the relation between various indexes of cognitive performance and the baseline blood pressure in 2 age groups (18 to 46 and 47 to 83 years) while accounting for covariates. In young and older subjects alike, measurements at enrollment of systolic and diastolic blood pressures and the blood pressure categories as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure predicted the decline in Visualization/Fluid abilities, but not Crystallized/Verbal, Memory, and Speed performance. Thus, younger compared with older adults were as vulnerable to the blood pressure-related decline in one aspect of their cognitive function.

While matter lesions on MRI of the brain are endemic among the elderly, for instance, with a frequency of more than two-thirds among Austrian community-dwelling volunteers aged 50 to 75 years. Confluent lesions correspond to incomplete ischemic destruction of deep periventricular or subcortical neuronal axons caused by microangiopathy. White matter lesions are forerunners of stroke and neurodegenerative disorders, including Alzheimer disease. For similar reasons as those outlined, experts long failed to recognize the role of blood pressure in the pathogenesis of white matter lesions. The CASCADE Consortium combined information from 9 cohort studies in 8 European countries involving 1625 nondemented men and women aged 65 to 75 years at enrollment. Measurement of the blood pressure at entry antedated magnetic resonance brain imaging by 5 to 20 years and was repeated at the time of the scan. In line with other longitudinal studies, the CASCADE Group confirmed that with adjustment for confounders, the prevalence and incidence of white matter lesions augmented with higher blood pressure in all countries with the exception of Germany, where the attrition of participants during follow-up had been more selective than in the other cohorts. The association between white matter lesions and change in blood pressure was particularly strong in patients with uncontrolled hypertension. It was graded and continuous for systolic blood pressure but J-shape for diastolic blood pressure. The Consortium speculated about various explanations that might underlie the J-shape relation with change in diastolic pressure, but in their analyses and interpretation they overlooked the most obvious one. With aging, isolated systolic hypertension becomes the major cardiovascular risk factor, with low diastolic blood pressure being a marker of arterial stiffening and cardiovascular deterioration.

In the concluding paragraph of their article, Elias et al speculated that the lowering of blood pressure by 20 mm Hg systolic or 10 mm Hg diastolic or from hypertensive to normotensive values might substantially contribute to the preservation of cognitive performance in the population as a whole. However, as stated by the CASCADE Consortium in their perspectives, only randomized clinical trials can prove the reversibility of a risk factor. Placebo-controlled trials of blood pressure-lowering medications, including thiazides,
β-blockers,8,9 or the angiotensin II type-1 receptor blocker candesartan,10 despite substantial blood pressure reductions, all failed to reveal protection against cognitive impairment or dementia. In the Perindopril Protection Against Recurrent Stroke Study,11 in patients with a history of cerebrovascular disease, the combination of perindopril with indapamide, but not perindopril in monotherapy, protected against poststroke dementia, a vascular type of cognitive decline. Until now, the double-blind placebo-controlled Systolic Hypertension in Europe trial (Syst-Eur) stands out as the only study of antihypertensive medications, which already after a median follow-up of 2.0 years demonstrated a 50% reduction in the incidence of all types of dementia, a benefit overwhelmingly caused by the prevention of Alzheimer disease.12 In Syst-Eur, the dihydropyridine calcium channel blocker nitrendipine was the main component of active treatment. After the double-blind trial had stopped in 1997, all patients were offered therapy with the same active medication. Median follow-up thereby increased to 3.9 years.13 The number of dementia cases doubled from 32 to 64 (41 with Alzheimer disease). Immediate compared with delayed antihypertensive therapy reduced the risk of dementia by 55% from 7.4 to 3.3 cases per 1000 patient-years.12

The Syst-Eur findings were in line with pharmacokinetic studies of nitrendipine.12 As other dihydropyridines, this compound crosses the blood–brain barrier and has specific binding sites in brain centers specifically affected by Alzheimer disease, including the cortex, thalamus, and hippocampus. Nitrendipine reduces the turnover of monoamine neurotransmitters, which are deficient in Alzheimer disease. Moreover, experimental studies suggest a pivotal role of intracellular calcium in the pathogenesis of Alzheimer disease. Free calcium ions are an intrinsic part of the intracellular machinery that drives injured or ischemic brain cells to apoptosis or cell death.13 Aging neurons extrude Ca$^{2+}$ in a less effective manner, which may sensitize them to pro-inflammatory and pro-oxidative substances.13 In a placebo-controlled trial in demented patients, the dihydropyridine nimodipine administered at a daily dose of 180 mg slowed the decline in the Mini Mental State Examination score.14

Whether blood pressure-lowering can prevent Alzheimer disease and to what extent calcium channel blockade provides specific protection against neurodegenerative dementia is issues with far-reaching implications for public health. Because of the worldwide demographic transition from high to low rates of birth and death, dementia is growing fast into one of the principal causes of major disability and mortality. In the United States, the prevalence of Alzheimer disease will quadruple over the next 50 years and affect 1 in every 45 Americans.15 Medical treatment of established dementia has only marginal benefit and is not cost-effective. Prevention is the only way to turn the tide. In view of the human suffering, clinical trials must be mounted to specifically address the question of whether blood pressure-lowering with or without calcium channel blockade can prevent Alzheimer disease. Almost 4 years ago, we wrote that this uncertainty is intolerable from the public health point of view and should not be allowed to continue. Elias4 and van Dijk10 generated persuasive new evidence highlighting the need of immediate action. Public research bodies, regulators, and the pharmaceutical industry should no longer remain indifferent, but take up the gauntlet. Quo usque tandem abstere patientia nostra?1

References

1 How long will you go on abusing our patience? (Marcus Cicero, First Catalinarian Intro, 63 BC).
Cognitive Impairment and Blood Pressure: Quo Usque Tandem Abutere Patientia Nostra?
Jan A. Staessen and Willem H. Birkenhager

_Hypertension_. 2004;44:612-613: originally published online October 4, 2004;
doi: 10.1161/01.HYP.0000145864.95630.20

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 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/44/5/612

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/