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Impact of Hypertension on Cognitive Decline and Dementia

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Dementia reduces a person's ability to perform their activities of daily living and is the leading cause of morbidity worldwide. While most preventive measures are ineffective in reducing dementia risk, active treatment of hypertension in middle-aged and older adults without dementia may reduce the incidence of dementia. Hypertension is associated with vascular dementia but may also affect the manifestations of Alzheimer disease. Observational studies support the association between hypertension and white matter lesions, hippocampal atrophy, and cognitive decline. Both increased and decreased blood pressure were related to the development of white matter lesions. Cohort studies showed that hypertension treatment and treatment duration were associated with lower cognitive decline. This review describes findings from randomized controlled studies on the effects of antihypertensives on cognitive decline. Only the Systolic Hypertension in Europe (Syst-Eur) trial using calcium-channel blockers demonstrated a significant reduction in dementia incidence. Further studies are required to evaluate the long-term benefits of antihypertensive treatment in dementia.

Key Words: Hypertension, Dementia, Prevention, White matter, Alzheimer disease

INTRODUCTION

Dementia is a disease resulting from acquired cognitive and functional impairments that reduce a person's ability to perform everyday activities and live independently.[1)] Dementia significantly affects individuals and their caregivers, families, communities, and societies.[2)] Dementia is currently the leading cause of morbidity worldwide, with an estimated annual global cost of US $818 billion.[2,3)]

The increasing longevity and number of older people worldwide are associated with a growing number of people living with dementia, particularly in lower and middle-income countries. Although most preventive measures are ineffective, active treatment of hypertension in middle-aged and older adults without dementia may reduce the incidence of dementia.[2)]

This paper provides an overview of hypertension and dementia, including recent evidence regarding hypertension treatment for dementia prevention.

HYPERTENSION AND ITS ASSOCIATION WITH COGNITIVE DECLINE

Several hypotheses purport to explain the relationship between hypertension and cognitive decline. The conventional theory is that hypertension is associated with cerebrovascular disease, leading to vascular or multi-infarct dementia. The International Workshop of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia (VaD) require the presence of cerebrovascular disease based on the detection of focal signs on neurologic examination, or evidence of cerebrovascular disease on brain imaging including large vessel infarcts, a strategically placed infarct multiple basal ganglia and white matter lacunes, extensive periventricular white matter lesions, or a combination of these radiological findings.[4)] VaD is likely if a person presents such evidence of cerebrovascular disease and manifests dementia symptoms, particularly if

there is a stepwise progression of cognitive deficits.

Long-term hypertension affects cerebral blood flow and metabolism as vessel injury causes thickening of the vessel walls and luminal narrowing via medial hyalinosis, resulting in stiffness and tortuous elongation.[5] The resulting endothelial dysfunction and blood-brain barrier alterations cause plasma protein leakage, oxidative stress, inflammation, and edema. These further compress brain tissue, contributing to hypoperfusion and demyelination.[6] Impaired cerebral autoregulation results in the loss of protective mechanisms, leading to a vicious cycle of neuronal injury. These disturbances in the blood-brain barrier cause diffuse white matter damage or leukoaraiosis. This is most evident in the periventricular white matter located at the boundary between different arterial territories, as these are the areas of the brain most susceptible to hypoperfusion.[7]

Although hypertension was traditionally considered to be associated with vascular dementia, it may also affect the manifestations of Alzheimer disease (AD). There is an overlap between markers of vascular injury and the hallmark pathology of AD. For example, blood-brain barrier dysfunction affects amyloid transport between the brain and periphery, leading to parenchymal and neurovascular amyloid deposition. AD pathology also causes vascular injury by damaging the blood vessel endothelium via Aβ-induced inflammation.[8]

Increasing evidence also suggests that sporadic AD is a vascular disorder caused by impaired cerebral perfusion rather than simply a neurodegenerative disorder.[9] Several epidemiological studies reported stroke, cardiac disease, and atherosclerosis to be the three most important risk factors for AD; these factors are also classic vascular risk factors.[10-12] Regional cerebral hypoperfusion is also a potential early marker of AD symptoms. Regional cerebral blood flow measurement by single-photon emission computed tomography (SPECT) showed that patients with mild cognitive impairment with significant hypoperfusion of the hippocampal-amygdala complex converted to AD within 3 years, while those with normal cerebral perfusion did not.[9,13]

Relationships among diabetes mellitus, AD, and vascular risk factors have also been reported. Insulin influences memory through receptors present in the hippocampus and medial temporal cortex. Insulin resistance and hyperinsulinemia lead to reduced brain insulin signaling, increased tau phosphorylation, and increased intracellular Aβ. Thus, diabetes increases the risk of both AD and VaD, regardless of the age at which diabetes occurs. The risk-enhancing mechanisms include the effects of insulin resistance described above; hyperglycemia-related increases in advanced glycation end products; and oxidative stress, inflammation, and macrovascular and microvascular injury. Interactions among lipids, lipoproteins, and Aβ play a critical role in Aβ production and clearance, whereas midlife obesity, hypercholesterolemia, and high systolic blood pressure additively increase the risk of dementia.[14]

In short, the vascular changes induced by hypertension increase brain susceptibility to ischemic-hypoxic damage in vulnerable white matter regions and may also promote AD neuropathology. Vascular changes and risk factors, especially diabetes, may be provoking and additive risk factors, while genetic factors such as apolipoprotein E (APOE) ε4 allele contribute to plaque formation.[15]

HYPERTENSION AND ITS ASSOCIATIONS WITH VASCULAR BURDEN ON NEUROIMAGING

There is a move towards routine structural neuroimaging with magnetic resonance imaging (MRI) for dementia evaluation owing to its greater sensitivity and ability to differentiate among dementia subtypes as compared with computed tomography.[4] Vascular burden is defined as the presence of many lacunae, strategic infarcts, substantial burden (> 25%) of white matter lesions, or combination of these findings. White matter lesions caused by long-standing hypertension are associated with cognitive impairment.[16]

The risk of severe white matter lesions is higher in people with poorly controlled hypertension than in those without or with treated hypertension. Increased systolic blood pressure is also associated with more severe periventricular and subcortical white matter lesions.[6] The Investigating Silent Strokes in Hypertensives: a Magnetic Resonance Imaging Study (ISSYS) cohort study of individuals with hypertension found that those with progression of periventricular white matter hyperintensities had a higher odds of cognitive decline compared to the odds for individuals with incident infarcts or microbleeds.[17] Diastolic hypertension was also associated with hippocampal atrophy compared to systolic hypertension, with hippocampal atrophy predictive of cognitive decline.[18] These observations support the association between hypertension and white matter lesions, hippocampal atrophy, and cognitive decline.

However, it is difficult to accurately determine the relative contributions of AD and cerebrovascular disease to a person's cognitive decline based on imaging findings alone.[2] For example, periventricular hyperintensities were correlated with age and were more severe in all dementia subtypes but were higher in patients with VaD than in those with dementia with Lewy bodies or AD.[19]

HYPERTENSION TREATMENT AND REDUCTION IN WHITE MATTER LESIONS OR DEMENTIA

An observational study of the efficacy of long-term hypertension

treatment observed an increased risk of late-life cognitive impairment and white matter lesions among individuals with hypertension at midlife.[20] Each year of hypertension treatment reduced the risk of dementia by 5%, with a lower cognitive decline observed for treatment durations of more than 5 years. However, studies on hypertension treatment efficacy have yielded conflicting results. The findings from randomized controlled studies of the effects of antihypertensives on the risk of cognitive decline are summarized in Table 1.

The Systolic Hypertension in Europe (Syst-Eur) trial compared the use of nitrendipine (with the possible addition of enalapril or hydrochlorothiazide) to reduce systolic blood pressure below 150 mmHg to placebo in terms of stroke and dementia outcomes. The trial was stopped prematurely after 2 years owing to a 42% decrease in fatal and non-fatal stroke and a 55% reduction in incident dementia.[16,21] Although the results of this trial showed great promise, subsequent studies have shown less positive results.

The SPRINT-MIND study randomized patients to receive intensive hypertension (systolic blood pressure < 120 mmHg) or standard (< 140 mmHg) treatments. The intensive control group had a significantly reduced risk of mild cognitive impairment but no reduction in the risk of dementia.[22]

In the treatment arm of the Hypertension in the Very Elderly Trial Cognitive Function Assessment (HYVET-COG), patients received indapamide with the possible addition of perindopril to target systolic and diastolic blood pressures of 150 and 80 mmHg, respectively. While the trial was stopped after 2-year follow-up due to a significant reduction in stroke and mortality incidence, there was no significant difference in the rate of cognitive decline or dementia between groups.[16] Similarly, while the Systolic Hypertension in the Elderly Programme (SHEP) trial used chlorthalidone (with the possible addition of atenolol and reserpine) to reduce systolic blood pressure to below 160 mmHg, active treatment reduced the incidence of cardiovascular events, but not those of dementia and disability.[23]

The Study on Cognition and Prognosis in the Elderly (SCOPE) randomized patients to receive candesartan or placebo and evaluated cardiovascular endpoints and cognitive function. No significant reduction in cardiovascular mortality, myocardial infarction, stroke or cognitive decline was observed between the treatment and placebo groups.[16,24] Finally, the Intensive Versus Standard Ambulatory Blood Pressure Lowering to Lessen Functional Decline in the Elderly (INFINITY) study randomized patients to receive intensive blood pressure-lowering (systolic < 130 mmHg) or standard treatment (target 145 mmHg). While intensive blood pressure lowering for 3 years significantly reduced the accumulation of subcortical white matter disease, it was not associated with differences in cognitive function.[25]

Overall, while these studies on antihypertensive treatment showed benefits in terms of cardiovascular risk, the effect on cognitive decline was less impressive. The choice of antihypertensive may be important, as the only study to convincingly show a cognitive benefit was the Syst-Eur study,[21] which utilized nitrendipine. As impaired intracellular calcium regulation contributes to brain

Table 1. Randomized controlled trials of hypertension treatment and its effect on the risk of cognitive decline

Trials (studies)	Follow-up duration (y)	Treatment vs. control	Blood pressure difference between treatment and control groups (mmHg)		Dementia incidences in treatment vs. control groups (per 1,000 patient-years)	Effectiveness of antihypertensive treatment in reducing dementia incidence and/or cognitive decline
			Systolic	Diastolic		
SYST-EUR[21]	2	Nitrendipine vs. placebo	-8.3	-3.6	7.7 vs. 3.8 (95% CI, 0–76)	Yes
SPRINT-MIND[22]	5.11	All classes but recommended thiazide-type diuretics as a first-line agent, loop diuretics in chronic kidney disease, and β-adrenergic blockers in coronary artery disease	-13.3	-	7.2 vs. 8.6 (HR = 0.83; 95% CI, 0.67–1.04)	Yes
HYVET-COG[16]	2	Indapamide +/- perindopril vs. placebo	-15	-5.9	33 vs. 38 (HR = 0.86, 95% CI, 0.67–1.09)	No
SHEP[23]	5	Chlorthalidone +/- atenolol +/- reserpine vs. placebo or reserpine	-11 to -14	-	No negative impact of blood pressure lowering on cognitive function (dementia incidence not measured)	No
SCOPE[24]	4.5	Candesartan vs. placebo	-3.2	-1.6	Dementia incidence not measured (95% CI, 0.08–0.38)	No
INFINITY[25]	3	ACEI or ARB, diuretics, CCBs, MRAs, beta-blockers vs. placebo	-15	-	No difference in cognitive endpoints (dementia incidence not measured)	No

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid receptor antagonist; HR, hazard ratio; CI, confidence interval.

aging and AD neuropathology, the benefit observed in this study may be due to the central nervous action of dihydropyridines.[3] The duration of these trials may also have been too short to observe any cognitive benefits.[16] Further studies may need to utilize other measures such as white matter lesions as a marker of cognitive decline or perform longer-term follow-up.

CONCLUSION

Hypertension is associated with cognitive decline and dementia and is a potential target for interventions to reduce dementia risk. While the treatment of hypertension shows great promise in reducing cardiovascular risk only the Syst-Eur trial using nitrendipine, a dihydropyridine calcium-channel blocker, demonstrated a significant reduction in dementia incidence. Further studies are required to evaluate the long-term benefits of antihypertensive treatment in dementia prevention.

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CONFLICT OF INTEREST DISCLOSURES

The researchers claim no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, HLN, SPT; Data curation, HLN, SPT; Writing_original draft, HLN, SPT; Writing_review & editing, HLN, SPT.

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