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COMMENT

Is it possible to prevent cognitive decline among middle-aged and older hypertensive individuals?

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Vascular dementia is the second leading cause of dementia after Alzheimer's disease. Having a stroke doubles the risk of developing dementia in the future, and recurrent events raise the prevalence of dementia to 30%. Subclinical cerebral small vessel disease (cSVD) is also an important contributor to cognitive impairment [1, 2]. cSVD affects small penetrating arteries, arterioles, capillaries, and venules and can be seen as a spectrum of different radiological markers that includes lacunar infarction, white matter hyperintensities, enlarged perivascular spaces, and microbleeds [3, 4]. The prevalence of cSVD is approximately 5% in subjects over 50, and it is present in almost everyone by the age of 90. Due to the aging population, vascular dementia is expected to increase in the following years. Therefore, the primary prevention of stroke and its recurrences is a priority strategy for the prevention of dementia.

Hypertension is the most important modifiable risk factor to prevent stroke, and it is strongly associated with the development of cSVD. The cerebral circulation shows structural and functional adaptations to chronic elevations of BP. At the early stages, the combination of hypertension and older age might increase blood–brain barrier permeability and white matter damage. In Table 1, we can observe the different possible mechanisms linking chronic hypertension to the risk of cerebrovascular diseases [4, 5]. Hypertension has also been more recently linked to Alzheimer's disease.

Major strokes and cSVD constitute major risk factors for vascular dementia. Mild cognitive impairment (MCI), often an intermediate phase between normal cognition and dementia, is characterized by reduced cognitive function in specific domains without an impact on activities of daily living. MCI is common in patients with hypertension, with an overall prevalence of 11.8–30% [6–8] and it increases the likelihood of progression to dementia or death compared with having no cognitive impairment.

In this issue of Hypertension Research, Bayang et al. [9]. identified different longitudinal trajectories of cognitive performance to provide interventions targeting the maintenance of cognitive function among middle-aged and older hypertensive subjects. They observed heterogeneity in longitudinal trajectories of cognitive performance in this cohort. This study focused on subjects aged 60.77 ± 0.28 years with hypertension at baseline. They showed that hypertensives with higher educational levels, moderate nighttime sleep duration, lower depressive symptoms, and alcohol consumption once a month and over were more likely to belong to the optimal stable executive function group. Unfortunately, this study does not provide information on the age of onset of hypertension or the years of exposure of these individuals to elevated BP.

Antihypertensive treatment and prevention of cognitive impairment

Despite the deleterious effects of hypertension, BP control remains suboptimal: Less than 50% of adults achieve adequate BP control. Recent data from the United States have shown that 17.3% of subjects with elevated BP were not treated, and 46.3% of those receiving treatment did not have a well-controlled BP [10]. In contrast, the percentage of treated and well-controlled hypertensive patients has reached a plateau. These data have worsened in recent years, probably because of low adherence and early discontinuation of antihypertensive treatment [10].

BP management is one of the three promising interventions to prevent cognitive decline, along with the increase in

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Table 1 Possible mechanisms linking chronic hypertension to the risk of cerebrovascular disease

Oxidative stress and endothelial dysfunction
Increased arterial stiffness
Renin-angiotensin system impairment
Cerebral small vessel disease (white matter lesions, lacunar infarcts, microbleeds)
• Blood–brain barrier damage and dysfunction • Neuroinflammation • Hypertension-induced vascular remodeling
Brain atrophy
Cerebral amyloid angiopathy

physical activity and cognitive training. A recent systematic review and meta-analysis showed that BP lowering with antihypertensive treatment compared with controls was significantly associated with a lower risk of incident dementia or cognitive impairment [11]. However, although the results from some randomized trials and observational studies are encouraging, they continue to be inconclusive, likely because clinical trials should have a longer follow-up time, and the intervention should start in midlife, which is difficult to carry out in clinical trials.

The optimal systolic BP target for the prevention of dementia is a subject of debate. In the Intensive vs. standard Ambulatory Blood Pressure Control on Cerebrovascular Outcomes in order people (INFINITIVE) [12], 199 participants (mean age 80.5 years) with white matter lesions were enrolled in this open-label trial with masked endpoints and randomly assigned to receive either intensive treatment (24 h systolic BP ≤ 130 mm Hg) or standard treatment (24 h systolic BP ≤ 145 mm Hg). No differences in cognitive function were observed, but there was less progression of vascular lesions (white matter intensities) in the group receiving intensive treatment than in the group receiving standard treatment. The SPRIND-MIND trial (Systolic Blood Pressure Intervention Trial. Memory and Cognition in Decreased Hypertension) [13] has shown that intensive systolic BP control of <120 mm Hg compared with a goal of <140 mm Hg reduced the risk of MCI. The brain magnetic resonance imaging substudy of SPRINT-MIND [14] showed that intensive systolic BP control was significantly associated with a smaller increase in white matter lesion volume than standard systolic BP control.

An especially relevant finding is that the relationship between BP and vascular dementia is stronger in midlife than in late life. A recent analysis from the Framingham Heart Study showed that the burden of cSVD increased with longer hypertension exposure [15], and data from the CARDIA [16] (Coronary Artery Risk Development in Young Adults) study have observed that after adjusting for several covariables (age, sex, race, education, diabetes, body mass index, smoking, alcohol intake, sedentary time, antihypertensive medication use and present systolic BP), early-onset hypertension was associated with worse cognitive test performance than late-onset hypertension. In a substudy of the 1946 British birth cohort (Insight 46) [17], high and increasing BP pressure from early adulthood to midlife was associated with increased white matter intensity volume and smaller brain volumes at 69–71 years. Suvila et al. [18]. also observed that early- but not late-onset hypertension is related to midlife cognitive function. Consistent with these results, a systematic review and meta-analysis of 209 prospective studies showed that midlife systolic BP > 130 mm Hg was associated with an increased risk of dementia.

According to the findings of previous studies, we propose an earlier cognitive screening in hypertension and an early improvement in the control rate of hypertension in middle-aged hypertensive subjects. More speculative would be whether some antihypertensive drugs would be more effective than others in preventing cognitive decline. A recent meta-analysis [19], including 14 studies ($n = 12849$ participants) from 6 different countries aged ≥ 50 years, suggested links between blood–brain barrier crossing renin-angiotensin drugs and less memory decline. Future studies should address whether the observed effect on memory can be attributed solely to medication with renin-angiotensin system inhibitors [20].

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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