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COMMENTARY

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Hypertension and cognition decline: Is there an ultimate link?

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The relationship between arterial hypertension and impairment of cognition is a matter of great importance since the prevention of hypertension, early intervention, and adequate control of blood pressure could modify the current high prevalence and global incidence of mild cognitive impairment (MCI) and dementia. MCI is considered to be an intermediate stage between the loss of normal cognitive aging and dementia, with maintenance of daily life activities. It is associated with a substantially increased risk of developing dementia. The impairment of cognition can occur in one or more areas that work in an integrated way, such as attention, perception, processing, memory, reasoning, visualization, problem solving, execution, and expression of information. A clinical diagnosis of dementia is defined when cognitive losses interfere with social or occupational activities.[1] The dementia of Alzheimer's disease is the most prevalent, followed by vascular dementia and mixed dementia.

There are many hypotheses linking elevated blood pressure to MCI or dementia such as endothelial dysfunction, reduced beta-amyloid clearance, excessive blood pressure dipping or nondipping during sleep, white matter disease (leukoaraiosis), association of hypertension and insulin resistance with abnormal insulin signaling in the brain, and pharmacological factors.[2]

Some questions remain unanswered, such as whether elevated blood pressure at all ages induces cognitive impairment. The Honolulu-Asia Aging Study showed that midlife systolic blood pressure was a predictor of reduced cognition function in later life,[3] as also did the National Heart, Lung, and Blood Institute Twin Study, which verified a 10-year change with lower cognition function and decreased brain volume in subjects with high systolic blood pressure in midlife.[4] Recently, the Atherosclerosis Risk in Communities (ARIC) Cohort also showed that midlife hypertension, prehypertension, diabetes and smoking were associated with an increased risk of dementia.[5]

However, it is still unclear if high blood pressure values in older people may contribute to cognitive impairment in the young, elderly and in the very old adults.[6] Some studies have shown the association of high blood pressure with reduced cognition,[7,8] others have shown the effect of the U[9,10] curve or even better cognition among centenarians with higher blood pressure,[11,12] probably due to the maintenance of cerebral perfusion in individuals with less regulation of this flow.

In this context, Wei et al,[13] in a study of a very large sample (6732) of Chinese Health and Retirement Longitudinal Survey (CHARLS) participants aged 45 years and over, without dementia, without stroke, cancer, renal failure or psychiatric problems, for blood pressure and episodic memory and executive function, found that treated but uncontrolled hypertension and high systolic blood pressure may be risk factors for cognitive decline in people aged 60-74. In people ≥75 years, untreated hypertension, treated but uncontrolled hypertension, and high pulse pressure may predict cognitive degeneration.

Higher pulse pressure denotes greater stiffness of the arteries, with a reduction of aortic compliance. A recent study showed a reduction of resting cerebral flow in the elderly with greater aortic stiffness, even without changes in vascular reactivity in the brain. In older people with mild cognitive impairment and apolipoprotein E4, there was a more intense reduction of flow in the temporal region.[14] Arterial stiffness was associated with beta-amyloid plaque deposition in the brain, independent of blood pressure or the presence of apoprotein E4.[15]

Questions are being raised about the greater importance of average blood pressure compared to the values of the pulse pressure (pulsatile component) or the variability of blood pressure as markers of risk for cognitive decline. An epidemiological study determined the association of higher pulse pressure with worse cognition in the elderly, without the influence of mean arterial pressure.[16] The variability of blood pressure monitored visit by visit showed greater association with cognitive decline than mean blood pressure in middle-aged and elderly individuals.[17] In a study of ambulatory blood pressure monitoring in subjects aged 65 years and over for 5 years, it was found that a greater variability of blood pressure during the daytime period was associated with worse cognitive function.[18]

Longitudinal studies have also shown conflicting results in detecting cognitive impairment in elderly individuals with high blood pressure,[19] but most of them support the view that the risk of dementia increases with arterial hypertension.[20,21]

Another unresolved question is whether treatment of hypertension could prevent cognitive decline, or even what would be the ideal goal of control in the elderly and very old to obtain this benefit.

By blocking the renin-angiotensin-aldosterone system, it is believed that aldosterone reduction and AT1 receptor blockade could have an impact on better cognition through the action of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs).[22,23] Furthermore, it is known that the AT2 receptors are responsible for reducing cellular proliferation and higher regeneration, besides vasodilatation. They are stimulated by ARBs, which can be seen as potential neural protective factors. The secondary analysis of data from a longitudinal study showed benefits with the use of diuretics, ACEIs, and ARBs.[24] A meta-analysis of 8 randomized trials involving the use of several antihypertensive drugs versus placebo did not show a benefit in the prevention of dementia with the treatment of hypertension in the elderly.[25] A more recent meta-analysis suggested a protective effect of calcium channels blockers (CBB) against the risk of dementia in elderly patients.[26] There could be a protective effect of CCBs by preventing calcium entry into cells, which would promote less apoptosis and cell death.

Comparing the control goal recommended by the Eighth Report of the Joint National Committee (JNC 8) for elderly people with SBP lower than 150 mm Hg,[27] with the goal recommended by the Systolic Blood Pressure Intervention Trial (SPRINT) of a SBP level lower than 120 mm Hg SPRINT,[28] there was less loss of cognition in individuals with more intense control, especially among black people.[29] However, it should be noted that this study was not randomized to control goals, with cognition being observed for 10 years in subgroups of individuals who had blood pressure in different control ranges.

A subanalysis of the SPRINT study, SPRINT Memory and Cognition in Decreased Hypertension (SPRINT MIND) answered some questions about the ideal goal of blood pressure to preserve cognition in cardiovascular high-risk, nondiabetic, stroke-free subjects. In the Alzheimer´s Association International Conference, the SPRINT MIND researchers presented preliminary results with a significant reduction in 19% in relative risk for MCI ($P = 0.01$), with nonsignificant reduction in probable dementia. Participants in the SPRINT trial that were submitted to magnetic resonance imaging (n = 454, 67.4%) had lower increase in volume of white matter lesions in the intensive treatment group ($P = 0.004$) after 3.98 years of follow-up. Total brain volume decreased in the intensive treatment and in the standard treatment groups, without significant difference.[30]

The current advance in research in this specific area is unquestionable. Although we do not yet know whether treatment of hypertension at any age, as well as the control of other known cardiovascular risk factors, would result in effective benefits in reducing MCI and dementia, and the ideal intensity of these interventions for all subgroups of patients, it is possible that this strategy will be as effective or even more effective in reducing the worldwide impact of dementia in the future than other specific medications that are being developed to prevent the advance of cerebral degeneration.

CONFLICT OF INTERST

None.

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