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Review Article

Arterial Hypertension and Cognitive Disorders: What are the Risks?

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Abstract: Prevention of cognitive disorders and dementia is a major public health issue. Several studies have found a significant association between the existence of arterial hypertension and the onset of cognitive disorders and dementia (vascular or Alzheimer's disease) several years later. Arterial hypertension causes vascular changes that affect blood flow and brain metabolism. Cognitive disorders may be related to the presence of focal ischemic lesions (infarction, lacunae) and/or chronic white matter ischemia (leucoaraiosis) related to damage to the small cerebral arteries (arteriosclerosis). Recent work also suggests that cerebral hypoxia and endothelial function abnormalities lead to changes in the blood-brain barrier leading to an accumulation of β-amyloid protein in the brain and the formation of responsible amyloid plaques. of Alzheimer's disease. Few therapeutic trials have included cognitive assessment and/or diagnosis of dementia. They all raise some important criticisms: cognition is never the primary endpoint, follow-up is too short to study dementia; the evaluation of cognitive functions is very summary, the number of patients "lost to sight" is significant and the subjects at risk of developing dementia are in very low proportion.

Keywords: Arterial hypertension, β-amyloid, blood pressure**,** dementia, leucoaraiosis.

INTRODUCTION

The term cognitive decline defines the acquired loss of cognitive functions, with or without repercussions in everyday life, whereas that dementia means an authenticated memory disorder, associated with at least one other disorder of higher functions and interfering with life activities daily. Dementia is one of the main pathologies of the elderly. Due to the aging of the population, the prevention of cognitive disorders and dementia represents a major challenge for years to come. In the absence of prevention, the number of people with dementia in the world likely to increase by 25 million in 2001 to 80 million in 2040 [1].

The identification and the management of the risk factors of these disabling conditions must therefore be a priority, in order to define the best tools for an early prevention. There are typically two types of dementia: Alzheimer's disease which is the most common form, and dementia vascular. In fact, several anatomopathological studies underline that a large number of dementias are not only of degenerative origin (Alzheimer's disease) or on the contrary vascular, but associate in reality the two types of lesions, defining "mixed dementia" [2]. Several epidemiological studies find an association between the presence of hypertension and the occurrence of cognitive disorders, highlighting the role of arterial hypertension (HTA) as a risk factor for dementia (vascular, Alzheimer or mixed) [3].

Epidemiological data

Most published cross-sectional studies report a statistical association between high blood pressure and lower cognitive performance, and this even in young subjects. Hypertension being, with age, the main risk factor for vascular dementias, and vascular dementias representing a quarter of dementias in Europe, we should expect higher prevalence of hypertension in demented subjects. In fact, cross-sectional studies show an association inverse between AP figures and prevalence of dementia and Alzheimer's disease, demented patients with means a lower blood pressure than the controls, the adjustment on hypotensive treatments and comorbidity factors not modifying the results.

Longitudinal studies are the most informative since they study the "chronic" impact of hypertension on cognitive functions. The majority of them indicates an association between hypertension blood pressure and cognitive impairment [4]. These studies were carried out within several different populations (general population or selected sample), aged on average 50 at age 81, with follow-ups ranging from 2 to 30 years. Globally, the results agree and find that hypertension at the average age of life (50–55 years) is a parameter strongly predictive of later cognitive deterioration (20–25 years later). Thus, the higher the initial blood pressure, the worse the cognitive functioning. ulterior. Hypertension not only puts you at risk cognitive decline but also at risk of dementia all causes combined.

Prevention of dementia by antihypertensive drugs

Few therapeutic trials have included an evaluation of the cognitive functions and/or the diagnosis of dementia. They all share certain criticisms: a follow-up too short to study the occurrence of dementia; an incomplete assessment of cognitive functions, loss of follow-up and inclusion of a small proportion of subjects at risk of dementia at onset of the test [5]. Four large therapeutic trials (SHEP, SYST-EUR, PROGRESS, HYVET) studied the effect of antihypertensive treatment on the prevention of dementia in comparison to the placebo.

The SYST-EUR study [6] was the first to demonstrate a significant reduction in the incidence of dementia 50% in the treated group compared to placebo. The benefit is observed for the prevention of dementia vascular but also Alzheimer's disease. The results indicate that treating 1000 patients for 5 years prevents 20 cases of dementia (95% CI = 7–33). The PROGRESS study [7,8] demonstrated a significant reduction severe cognitive decline of 19% (95% CI = 4–32%, p = 0.01) with antihypertensive therapy in patients with history of cerebrovascular accident. The risk of dementia was reduced by 12% in the treatment group (95% CI = 8–28%) and 34% in patients who had recurrent strokes (95% CI = 3–55%). The reduction of dementia was significant under dual therapy (reduction of 23%; 95% CI = 0–41%) but not on monotherapy (8%; 95% CI = 48–21%), highlighting the role of lower tension.

Finally, the results of the HYVET study [9] also go in the same direction and emphasize a reduction in the incidence of dementia of 14% in the treated group (HR 0.86 [95% CI 0.67–1.09], p=0.21). However, this reduction does not reach the significance level probably due to a lack of statistical power related to premature cessation of the study after 2 years (due to a benefit on the total mortality). All these data were grouped together in a meta-analysis including 16,595 subjects. The results indicate a significant 13% reduction in the risk of dementia on antihypertensive treatment compared to placebo

Benefit of cognitive disorder screening in the hypertensive elderly

In practice, it appears essential to identify, among hypertensive patients, subjects with early cognitive disorders in order to optimize their treatment. This comprises carrying out a specialized memory assessment which makes it possible to identify and diagnose the origin of the disorders (Alzheimer's disease [10], vascular dementia [11], mixed dementia; other dementias: Lewy body disease [12], fronto-temporal dementias [13]. Depending on the diagnosis, symptomatic treatments can be proposed (drugs anticholinesterases, NMDA receptor antagonists, serotonin reuptake inhibitors), as well as taking non-medicinal load (cognitive stimulation, speech therapy, passage to the nurse to deliver medication, aids home. Finally, an analysis of risky situations (adherence to medication, driving, management budget, home gas, isolation.) is necessary in order to consider preventive measures.

After 80 years it is recommended to assess cognitive functions in elderly hypertensives using the MMSE test" due to the risk of onset of dementia and to assess the risk of poor adherence to treatment [14]. Identification of cognitive disorders may involve a test faster like the MIS (Impairment Screen Memory) which consists of repeating 4 words written on a sheet: TABLE, TULIP, TRAIN, OAK, immediately and 10 minutes later. Forgetting one of the words, despite a clue (e.g., "what was the name of the tree?") should do suspect cognitive disorders and justifies a specialized complementary assessment [15].

Physiopathological mechanisms

Cerebral infarctions and cerebral lacunae

Hypertension is the cause of vascular changes that affect blood flow and brain metabolism. The cognitive disorder may be related to the presence of focal ischemic lesions (infarction, gaps). The occurrence of a stroke multiplies the risk of dementia by a factor of 2 to 5, which makes it the most important risk factors for dementia [16]. Of even small infarcts not clinically detectable could precipitate patients into clinically overt forms of dementia. Thus, in the Nun study the presence of small lacunar infarcts at autopsy multiplied by 20 the risk of dementia in people with neuropathological criteria for Alzheimer's disease [17]. Most often, it is the summation of vascular lesions and of degenerative lesions which will contribute to an expression anticipated cognitive impairment, reaching the threshold of dementia earlier [18].

White matter hyperintensities (HSB)

HSB (or leukoaraiosis) correspond to areas of high signal visible on MRI on T2-weighted images, located in the white matter [19]. The mechanisms leading to HSB involve the degeneration of small caliber cerebral arteries as well as the decrease in flow cerebral blood which are consequences of hypertension

(arteriosclerosis). These lesions are indicative of chronic ischemia linked to damage to the small cerebral vessels [20]. Numerous studies have shown that the HSB load was associated with cognitive impairment or dementia [21] partly linked to the alteration of the cortico-subcortical circuits. The severity of white matter lesions is defined on MRI. A severe grade multiplies the risk dementia by 4, a moderate grade multiplies this risk by 2 [22].

Cerebral hypoxia

Several recent experimental studies suggest that cerebral hypoxia linked to high blood pressure could also promote the formation of amyloid plaques at the origin of the occurrence of Alzheimer's disease. Thus, hypoperfusion brain could stimulate a beta-secretase enzyme (BACE1) promoting the aggregation of beta-amyloid peptide and the formation of intracerebral plaques [23].

Endothelial function abnormalities

The abnormalities of endothelial function observed in hypertensives can lead to changes in the blood-brain barrier which can cause abnormalities in the exchange of transport molecules (LRP [low density lipoprotein receptor-related protein]) of the protein b-amyloid [24]. These changes lead to a decrease clearance of b-amyloid protein and impaired its cerebral elimination. This accumulation of protein intracerebral b-amyloid will then promote its aggregation and the formation of amyloid plaques in the brain causing of neuronal death [25].

Inflammation

Inflammation is a process common to vascular and neurodegenerative pathologies [26]. Indeed, inflammation seems to play an important role in the regulation of different isoforms of the protein precursor protein amyloid (APP). Thus, interleukin-1 activates the synthesis of APP and its excess production could promote the synthesis of neurotoxic amyloid peptide [27]. Moreover, the presence of cerebrovascular lesions promotes the activation of microglial cells and the synthesis of pro-inflammatory cytokines which participate in the process of neuronal death [28].

CONCLUSION

There are very solid pathophysiological and epidemiological arguments in favor of the association between hypertension and cognitive disorders. Hypertension promotes cognitive disorders via presence of cerebral vascular lesions (infarction, lacunae, leucoaraiosis) but also probably via a direct effect on the formation of intracerebral amyloid plaques. The studies randomized against placebo are few in number because they are difficult to achieve, however, the majority of them indicate prevention of cognitive impairment with antihypertensive drugs.

REFERENCES

1. Nichols, E., Steinmetz, J. D., Vollset, S. E., Fukutaki, K., Chalek, J., Abd-Allah, F., ... & Liu, X. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health*, *7*(2), e105-e125.
2. Karantzoulis, S., & Galvin, J. E. (2011). Distinguishing Alzheimer's disease from other major forms of dementia. *Expert review of neurotherapeutics*, *11*(11), 1579-1591.
3. Sierra, C. (2020). Hypertension and the risk of dementia. *Frontiers in cardiovascular medicine*, 31, 7-5.
4. Mishra, N., Mohan, D., Fuad, S., Basavanagowda, D.M., Alrashid, Z.A., Kaur, A., Rathod, B., Nosher, S., Heindl, S.E. (2020). The Association Between Hypertension and Cognitive Impairment, and the Role of Antihypertensive Medications: A Literature Review. *Cureus*, *12*(12), e12035.
5. Walker, V. M., Davies, N. M., Martin, R. M., & Kehoe, P. G. (2020). Comparison of antihypertensive drug classes for dementia prevention. *Epidemiology (Cambridge, Mass.)*, *31*(6), 852.
6. Forette, F., Seux, M. L., Staessen, J. A., Thijs, L., Birkenhäger, W. H., Babarskiene, M. R., ... & Fagard, R. (1998). Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *The Lancet*, *352*(9137), 1347-1351.
7. Tzourio, C., Anderson, C., & Chapman, N. (2003). PROGRESS Collaborative Group. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Archives of internal medicine*, *163*(9), 1069-1075.
8. Arima, H., & Chalmers, J. (2011). PROGRESS: prevention of recurrent stroke. *The Journal of Clinical Hypertension*, *13*(9), 693-702.
9. Peters, R., Beckett, N., Forette, F., Tuomilehto, J., Clarke, R., Ritchie, C., ... & Bulpitt, C. (2008). Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *The Lancet Neurology*, *7*(8), 683-689.
10. Bourin, M. (2017). How to diagnose an Alhzeimer disease? *Theranostics Brain Disorder*, *1*(4), 555-566
11. Bourin, M. (2023). Vascular Dementia: Definitions, Origins, Symptoms, Diagnosis and Treatments. *SAR J Psychiatry Neurosci*, *4*(1), 1-4.
12. Bourin, M. (2018). Lewy body dementia : a review. *J Neurosci Neurosurg*, *1*(2), 108.
13. Bourin, M. (2019). The frontotemporal dementias; an update. *J Neurosci Neurosurg*, *2* (1), 1-4
14. Sierra, C. (2020). Hypertension and the Risk of Dementia. *Front Cardiovasc Med. 31*, 7-5

15. Velayudhan, L., Ryu, S. H., Raczek, M., Philpot, M., Lindesay, J., Critchfield, M., & Livingston, G. (2014). Review of brief cognitive tests for patients with suspected dementia. *International psychogeriatrics*, *26*(8), 1247-1262.
16. Iadecola, C., & Gottesman, R. F. (2019). Neurovascular and cognitive dysfunction in hypertension: epidemiology, pathobiology, and treatment. *Circulation research*, *124*(7), 1025-1044.
17. Snowdon, D. A., Greiner, L. H., Mortimer, J. A., Riley, K. P., Greiner, P. A., & Markesbery, W. R. (1997). Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. *Jama*, *277*(10), 813-817.
18. Gorelick, P. B., Scuteri, A., Black, S. E., DeCarli, C., Greenberg, S. M., Iadecola, C., ... & Seshadri, S. (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *stroke*, *42*(9), 2672-2713.
19. Wardlaw, J. M., Valdés Hernández, M. C., & Muñoz-Maniega, S. (2015). What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *Journal of the American Heart Association*, *4*(6), e001140.
20. Iadecola, C., & Davisson, R. L. (2008). Hypertension and cerebrovascular dysfunction. *Cell metabolism*, *7*(6), 476-484.
21. SHEP Cooprative Research Group. (1991). Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. *Jama*, *265*, 3255-3264.
22. Zeng, W., Chen, Y., Zhu, Z., Gao, S., Xia, J., Chen, X., ... & Zhang, Z. (2020). Severity of white matter hyperintensities: lesion patterns, cognition, and microstructural changes. *Journal of Cerebral Blood Flow & Metabolism*, *40*(12), 2454-2463.
23. Cai, Z., Liu, Z., Xiao, M., Wang, C., & Tian, F. (2017). Chronic cerebral hypoperfusion promotes amyloid-beta pathogenesis via activating β/γ-secretases. *Neurochemical Research*, *42*, 3446-3455.
24. Storck, S. E., Meister, S., Nahrath, J., Meißner, J. N., Schubert, N., Di Spiezio, A., ... & Pietrzik, C. U. (2016). Endothelial LRP1 transports amyloid-β 1–42 across the blood-brain barrier. *The Journal of clinical investigation*, *126*(1), 123-136.
25. Ma, C., Hong, F., & Yang, S. (2022). Amyloidosis in Alzheimer's disease: Pathogeny, etiology, and related therapeutic directions. *Molecules*, *27*(4), 1210.
26. Moyse, E., Krantic, S., Djellouli, N., Roger, S., Angoulvant, D., Debacq, C., ... & Aidoud, A. (2022). Neuroinflammation: a possible link between chronic vascular disorders and neurodegenerative diseases. *Frontiers in Aging Neuroscience*, 352.
27. Kinney, J. W., Bemiller, S. M., Murtishaw, A. S., Leisgang, A. M., Salazar, A. M., & Lamb, B. T. (2018). Inflammation as a central mechanism in Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *4*, 575-590.
28. Ballaz, S., & Bourin, M. (2023). Anti-Inflammatory Therapy as a Promising Target in Neuropsychiatric Disorders. In *Neuroinflammation, Gut-Brain Axis and Immunity in Neuropsychiatric Disorders* (pp. 459-486). Singapore: Springer Nature Singapore.