

Cardiovascular Alterations in Patients with Dementia

Abstract

Hypertension is a major risk factor for vascular cognitive impairment (VCI) and for Alzheimer disease (AD). In this mini review we discuss about the impact of hypertension on the brain. Alzheimer disease and vascular cognitive impairment are the first and second most frequent causes of dementia in the elderly people. Evidence shows that these conditions share common pathogenetic mechanisms. Vascular changes induced by hypertension increase the susceptibility of the brain to ischemic-hypoxic damage and promote the expression of Alzheimer disease neuropathology. The possible benefits of pharmacological blood pressure control on cognition justify prompt intervention, together with diet and exercise, especially in younger patients.

Keywords: Hypertension; Vascular cognitive impairment; Alzheimer disease

Abbreviations: HTN: Hypertension; BP: Blood Pressure; VCI: Vascular Cognitive Impairment; AD: Alzheimer Disease; SVD: Small Vessel Disease; RAAS: Renin-Angiotensin-Aldosterone System

Introduction

Hypertension (HTN) is a major cause of morbidity and mortality [1] and represents the most important risk factor for stroke, the second cause of death in the world and a major cause of long-term disability [2]. High blood pressure (BP) affects target organs, one of the most susceptible being the brain [1]. Hypertension is a major risk factor for vascular cognitive impairment (VCI) and for Alzheimer disease (AD), the most frequent causes of dementia in the elderly [3]. Continuous elevation in blood pressure has progressive effects on the structure and function of cerebral arteries determining adaptive changes like remodeling, aiming to decrease the mechanical stress on the arterial wall [4]. Remodeling could be hypertrophic or eutrophic and reduces the vessels' lumen increasing the vascular resistance and represents a potential risk factor for cardiovascular and cerebrovascular disease [5].

Old hypertension also induces an increase in the stiffness of large arteries which is a good predictor of cognitive decline and stroke and is associated with silent brain lesions [3,6]. HTN is a major risk factor for atherosclerosis. Increase in BP increases the odds of complex aortic atherosclerosis, predictive of ischemic strokes [7]. Atherosclerotic lesions are localised at the site of turbulence of the flow like the carotid bifurcation and the vertebrobasilar system and less frequently in intracranial arteries. Stroke can be produced by releasing fragments from atherosclerotic plaques (artery-to-artery embolism) or by rupture and hemorrhage with acute cerebrovascular occlusions.

HTN also provokes small vessel disease (SVD) in which the most frequent pathological substrate is arteriolosclerosis [8], affecting the deep hemispheric white matter and basal ganglia. One of the pathological features of arteriosclerosis is lipohyalinosis [8] and in advanced lesions rupture of the vessel

with microscopic or macroscopic hemorrhages disposed typically in basal ganglia or thalamus. Capillary rarefaction induces lesions in the periventricular white matter.

Brain alterations underlying VCI

VCI includes a spectrum of cognitive alterations due to cerebrovascular factors, ranging from mild to full blown vascular dementia impairing the daily life's activities [3]. A major cause of cognitive impairment is stroke. Having a stroke doubles the risk of dementia (poststroke dementia) [3]. The risk of VCI is increased in patients with no history of stroke but with brain infarcts (silent infarcts) at imagistic investigations. Strategic-infarct dementia is produced by a single stroke affecting a region important for cognition like the frontal lobe or the thalamus [3]. Multi-infarct dementia can also result from multiple strokes destroying large amounts of brain tissue [3]. SVD is a major cause of VCI, being responsible for up to 45 % of dementia cases [3].

Neuropathological alterations caused by cerebral SVD linked with VCI

Lacunar infarcts: Are rounded, < 20 mm diameter lesions, founded more frequently in the basal ganglia, associated with SVD and a strong predictor of VCI [11]. They are caused by acute occlusion of small perforating cerebral arteries or embolism from upstream vessels [12]. Recent studies show the possibility that blood-brain barrier (BBB) alterations are early pathogenic events, their occurrence being multifactorial [12].

Mini Review

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Microinfarcts: SVD is also associated with cerebral microinfarcts, small size < 1 mm diameter, invisible ischemic lesions, very frequent in the elderly [14]. Microinfarcts are common in patients with vascular or mixed dementia, also being an independent predictor of VCI. Location and number of the microinfarcts are the most important determinants of cognitive impairment, the cortical location being closely associated with dementia [14].

Cerebral hemorrhages: SVD produces micro or macrobleeds. Cerebral microbleeds are perivascular hemorrhages (2-10 mm) that can be detected histologically at autopsy or at magnetic resonance imaging (MRI) [15]. Microbleeds, presented in 10-20% of the elderly are an independent predictor of cognitive decline [15]. The most important risk factor of microbleeds is HTN, in this situation microhemorrhages being especially located in thalamus, cerebellum, basal ganglia and brain stem [16] and frequently associated with cerebral amyloid angiopathy, in which situation having a lobar distribution [15]. HTN also produces large cerebral hemorrhages, typically located in thalamus or the basal ganglia.

Diffuse white matter alteration: Or leukoararoyosis, represents a reduction in white matter density [3,8]. HTN precedes its development [13] and is often present in the periventricular white matter, resulting from hypoxia-hypoperfusion. This region is more vulnerable to hypoperfusion being located at the boundary between separate arterial territories [10]. Endothelial dysfunction and BBB alterations caused by HTN contribute to hypoperfusion and demyelination [12].

AD and HTN

AD and VCI are the first and second most frequent causes of dementia in the elderly [3]. Evidence shows that these conditions share common pathogenetic mechanisms [9]. Major cardiovascular risk factors are also risk factors for AD. HTN in middle age doubles the risk of occurrence of AD later in life and also increases the progression of dementia [17].

Up to 50% of patients with dementia have both vascular (SVD) and neurodegenerative lesions (amyloid plaques and neurofibrillary tangles) [18]. Association between HTN and AD may be additive or synergistic, producing a more severe cognitive degradation [9]. Necroptotic studies of patients with AD showed more atherosclerotic lesions in cerebral vessels associated with more amyloid plaques and neurofibrillary tangles [19,20]. Brain of hypertensive patients has increased amyloid plaques and neurofibrillary tangles [21]. Blood β -amyloid ($A\beta$), involved in the pathogenesis of AD, is elevated in patients with VCI, contributing to vascular dysfunction [22,23]. Elevated diastolic BP in middle age are associated to an increase in AD risk later [24]. Studies suggest that HTN could be a promoter of the development of AD, mechanisms involved being impairment of vascular clearance of $A\beta$, with increasing accumulation in vessels and brain, and increasing of the cleavage of $A\beta$ from the precursor protein. These produce growth of $A\beta$ concentrations in brain and blood vessels, accelerating this dysfunction.

Prevention of stroke and dementia by HTN treatment

HTN control has an important impact on the incidence of stroke, for each 10 mm Hg decrease in systolic BP there was a one-third decrease in stroke risk [2]. HTN treatment is very important

also for prevention of poststroke dementia [3]. All classes of antihypertensive drugs are effective³. An American Heart Association statement recommends blood pressure control in patients poststroke (Class I, B) and also treatment in the younger of the elderly (Class IIa, B) [3]. A study reported a progressive cognitive decline for values of systolic BP between 120-140 mm Hg [25], suggesting need for treatment at prehypertensive levels. Calcium-channel blockers and inhibitors of renin-angiotensin-aldosterone system (RAAS) increase $A\beta$ removal from the brain and protect against cognitive impairment in animal models [26,27]. Some observations suggest that angiotensin converting enzyme (ACE) activity is augmented in AD patients and that ACE may degrade $A\beta$ [27]. The possible benefits of pharmacological blood pressure control on cognition justify prompt intervention, together with diet and exercise, especially in younger patients [28].

Conclusion

Despite important progresses in controlling its impact on morbidity and mortality, HTN remains one of the most devastating diseases, with profound impact on the brain, contributing to stroke and dementia, diseases projected to have a greater public health impact because of population aging. Cerebral vessels are key targets of HTN, vascular changes induced by HTN increasing the susceptibility of the brain to ischemic-hypoxic damage and promoting the expression of AD neuropathology. Although current treatment of HTN have dramatically reduced stroke morbidity and mortality, the role in prevention of late-life dementia has been difficult to assess. Whatever the influence on cognition, the benefits of BP control justify early intervention.

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