Hypertension Research (2023) 46:1344–1346
https://doi.org/10.1038/s41440-023-01246-6

COMMENT

Contributions of neuroimaging to the knowledge of the relationship between arterial hypertension and cognitive decline

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Keywords Hypertension · Cerebral small vessel disease · Cognitive decline · Neuroimaging · Blood–brain barrier dysfunction

Received: 23 January 2023 / Revised: 14 February 2023 / Accepted: 17 February 2023 / Published online: 8 March 2023

The relationship between hypertension and brain structure and functions is not completely known and current evidence suggest that several pathological factors can interact [1]. Hypertension can produce vascular and functional changes in larger and small cerebral vessels in the brain, and cerebral small vessels and arterioles are more vulnerable to the mechanical stress associated with hypertension [2] (Fig. 1). It is relevant to highlight the strong relationship between arterial hypertension and cerebral small vessel disease (cSVD); the characteristic findings of cSVD in Magnetic Resonance Imaging (MRI) include lacunar infarcts, white matter hyperintensities (WMH) cerebral microbleeds (CMB), enlarged perivascular spaces, and brain atrophy [3, 4]. On the other hand, chronic hypertension induces a rightward shift in the autoregulatory curve, and consequently, an increment of vulnerability to sudden changes in blood pressure, resulting in ischemia or increased risk of brain hemorrhage.

Endothelial dysfunction (ED) is considered to appear at an early stage of cSVD, before any radiologic signs become evidence. Cerebral ED may be measured by transcranial Doppler, but functional transcranial Doppler has major limitations in terms of operator variability [4]. Blood–brain barrier (BBB) is a dynamic interface between the cerebral circulation and the central nervous system, and an intact BBB usually acts to protect the brain. Recent evidence suggested that acute and chronic hypertension could produce BBB damage, which is crucial for blood pressure regulation. The mechanisms involved in the breakdown of the BBB include brain sympathetic nervous system (SNS) activation, and brain renin-angiotensin system (RAS) activation, associated with endothelial injury, oxidative stress, and inflammation. Usually, circulating Angiotensin II (Ang II) does not cross the BBB, but elevated circulating levels during hypertension can produce disruption of the BBB integrity, allowing access of circulating Ang II [5, 6]. On the other hand, all components of Renin-Angiotensin System (RAS) are locally produced in several brain regions and could contribute to hypertension-induced brain injury. Some experimental data suggest that RAS activation is in relationship with hypertension-induced cognitive impairment.

Hypertension and neuroimaging studies

Neuroimaging studies could represent a relevant role in advancing our knowledge about the link between hypertension and cognitive impairment [7]. WMH seem to be more prevalent in elderly individuals with atherosclerosis and hypertension, but its pathogenesis involves multiple mechanisms. Covert vascular brain infarcts (CVBI) are much more frequent in the general population than clinical stroke, especially in the older population. The detection of CVBI in MRI have major clinical significance and can predict an increased risk of ischemic or hemorrhagic stroke, dementia, and death. A systematic review and meta-analysis of 94 prospective studies [8], including 14,529 participants for WMH, 15,693 participants for CMB and 34,857 participants for PVS have observed significant association of

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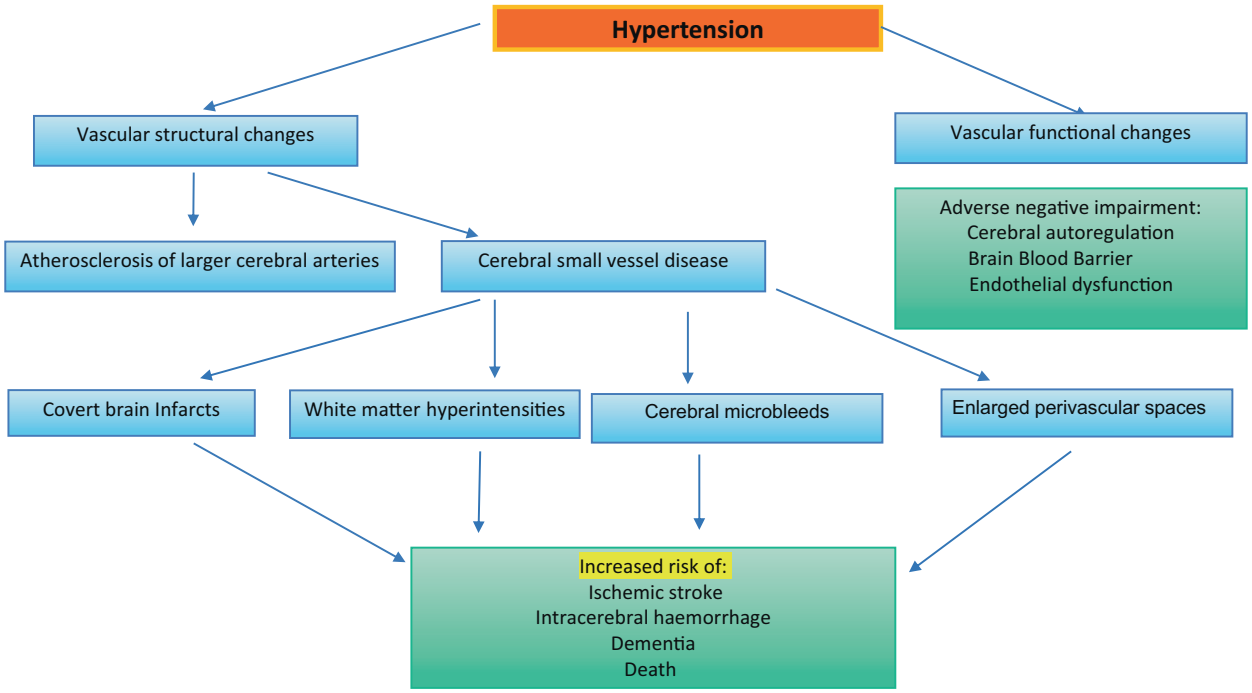

Fig. 1 Hypertension, cerebral small vessel disease and radiological makers of vascular brain injury on magnetic resonance imaging (MRI)

WMH burden, CVBI and CMB with increased risk of incident stroke, both ischemic stroke (risk more than doubled) and intracerebral hemorrhage (risk more than tripled). On the other hand, WMH burden, CBI and CMB were all associated with increased risk of death (Hazard ratio between 1.5 and 2.0). MRI markers of CVBI are correlated with each other, and it is no possible to determine if observed associations are independent of other MRI markers of vascular brain injury. Recent studies have observed that different patterns of subcortical WMH visually identified on MRI might have different impacts on cognitive impairment [9].

Although radiological studies have made great progress, more precise techniques are required to detect the pathogenesis of cSVD. Newer imaging techniques suggest that WMH represents the end of a continuum spectrum of white matter injury [1]. Emerging evidence shows significant microstructural changes on diffusion tensor imaging (DTI) before the appearance of WMH. A recent study has observed that the effect of older age, hypertension, and female gender on greater WMH were mediated by diffusion changes seen in DTI [10].

In the issue of Hypertension Research, Liao et al. [11] have investigated the alterations and diagnostic efficiency of regional homogeneity (ReHo) and functional connectivity (FC) in hypertension patients with cognitive impairment. They have studied 62 hypertensive patients with cognitive impairment (HTN-CI), 59 hypertension patients with normal cognition (HTN-NC), and 58 healthy controls (HCs). The main findings of this study were that HTN-CI was associated with decreased ReHo and increased FC mainly in the left posterior cingulate gyrus, postcentral gyrus, insula compared to HTN-NC and HC. These findings may contribute to unveiling the underlying neuropathological mechanism of HTN-CI.

Hypertension, vascular brain injury, and cognitive decline

Hypertension is one of the main risk factors for vascular dementia and it is also associated with Alzheimer disease. Subclinical cSVD is frequently identified in neuroimaging studies and is thought to play a relevant role in the pathogenesis of cognitive disorders. A large number of observational studies have shown a strong link between hypertension and different adverse cognitive outcome [12, 13]. Although the acute cerebral effects of hypertension have been recognized for a long time, the chronic impact of hypertension on cognition and brain homeostasis is not very well known. A recent study has shown brain functional connectivity alterations in patients with hypertension in whom structural MRI does not show signs of macroscopic damage [14].

A strong relationship between hypertension during midlife and cognitive decline in later adulthood has been observed. To assess these changes, it is necessary to use tools with sufficient sensitivity to detect mild cognitive impairment (MCI), an intermediate phase between normal cognition and dementia, that is characterized by reduced

cognitive function in specific domains without impact on activities of daily living. MCI is common in patients with hypertension, and it increases the likelihood of progression to dementia or death compared with no cognitive impairment. An interesting study carried out in 1946 British birth cohort (Insight 46) [15] among young to middle aged participants, has shown that higher blood pressure (BP) or greater increases in BP during the 4th and the 6th decade were associated with higher WMH and smaller brain volumes during the 6th and 7th decade. However, BP during young to middle-aged was not associated with brain amyloid β deposition in late adulthood.

In summary, most of cSVD MRI markers, strongly associated with hypertension are related to cognitive impairment, independently of age. Neuroimaging studies could represent a relevant role in advancing our knowledge about the link between hypertension and cognitive impairment. Although neuroradiological studies have made great progress, more precise techniques are required to improve our knowledge about the deep mechanisms underlying the relationship between arterial hypertension and cognitive decline.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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