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COMMENT

Possible relationship between primary aldosteronism and small vessel disease

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Primary aldosteronism (PA) is characterized by the autonomous overproduction of aldosterone from the adrenal cortex and is one of the most frequent causes of secondary hypertension [1]. Aldosterone exerts its influence not only by promoting sodium retention in renal tubules but also through direct effects on various organs, including the heart, kidneys, adipose tissue [2, 3], and blood vessels, inducing inflammation in these tissues [4]. Patients with PA face an elevated risk of cardiovascular disease, stroke, dementia, and chronic kidney disease when compared to patients with essential hypertension (EH) [5, 6]. It is crucial to initiate specific treatments as soon as possible aimed at correcting hypertension and aldosterone activity, such as mineralocorticoid receptor antagonists (MRBs) or adrenalectomy [1, 7, 8].

Stroke is caused by vessel occlusion or hemorrhage in the brain, associated with classical risk factors of vascular disease such as hypertension, smoking, and diabetes. Dynamic interactions between endothelial cells, vascular smooth muscle, astrocytes, microglia, oligodendrocytes, neurons, and the surrounding tissue matrix is recognized as the neurovascular unit and is a minimal unit for brain function [9, 10]. For this unit to function properly, microvessels play a critical role, and their dysfunction is termed cerebral small vessel disease (SVD). SVD is a key concept in the pathophysiology of a wide range of brain disorders, including stroke and Alzheimer's disease [10]. One vital role of these microvessels is maintaining the blood–brain barrier. Various factors, including ischemia, hypertension, hyperglycemia, or amyloid angiopathy, can induce endothelial dysfunction and break tight junctions, leading to the leakage of red blood cells, which is known as cerebral microbleeds (CMBs). CMB is one of the classical MRI-related signs of SVD and is associated with a risk of future stroke [11]. Other findings associated with SVD include white matter hyperintensities (WMH), lacunes, and enlarged perivascular spaces (EPVS).

While SVD is recognized as a critical factor in discussions about stroke and is linked to hypertension, the connection between PA and SVD remains unclear. In this context, Lee et al. assessed brain MRI findings in survivors of intracranial hemorrhage with hypertension, dividing them into PA ($n = 21$) and EH ($n = 69$) groups [12]. Their results showed that the PA group had a significantly higher risk of CMBs and EPVS compared to the EH group. Furthermore, they demonstrated a linear relationship between the degree of EPVS and log ARR (i.e., plasma aldosterone-to-renin ratio).

It is already known that patients with PA have a higher risk of stroke compared to patients with EH. However, this study may provide novel insights into how aldosterone activity affects the brain and increases the risk of stroke. Similarly, Yuan et al. have shown that high ARR is an independent risk factor for WMH in hypertensive patients [13]. In mice, aldosterone administration was shown to induce oxidative stress and inflammation through vascular endothelial cells in the brain, which could be prevented by spironolactone [14]. The renin-angiotensin-aldosterone system is considered a potential biomarker for SVD in the brain.

This study has several limitations. First, it was a small observational study, and causality and external validity need further verification. Second, some important confounders, such as antihypertensive medications, statins, and smoking

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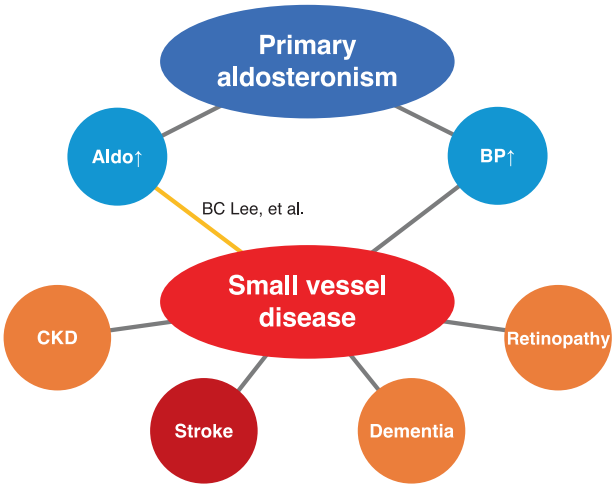

Fig. 1 Possible relationship between primary aldosteronism and small vessel disease. Schematic diagram for the known and inferred association between primary aldosteronism and small vessel disease is shown. Aldo aldosterone, BP blood pressure, CKD chronic kidney disease

status, were not adjusted. In addition, this study did not assess the effects of PA treatments, such as adrenalectomy or MRBs. It would be interesting to investigate whether these treatments can reduce the risk of SVD-related MRI findings among patients with PA.

Patients with PA have a higher risk of dementia, which is also associated with SVD, when compared to those with EH [6]. Besides, the concept of SVD extends beyond the brain, as similar structures can be observed in other organs like the kidneys and retinas [15]. Further understanding of the relationship between SVD and aldosterone may help us understand other neurological diseases and organ damage beyond stroke among PA (Fig. 1).

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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References

1. Naruse M, Katabami T, Shibata H, Sone M, Takahashi K, Tanabe A, et al. Japan Endocrine Society clinical practice guideline for the diagnosis and management of primary aldosteronism 2021. Endocr J. 2022;69:327–59.
2. Haze T, Ozawa M, Kawano R, Haruna A, Ohki Y, Suzuki S, et al. Effect of the interaction between the visceral-to-subcutaneous fat ratio and aldosterone on cardiac function in patients with primary aldosteronism. Hypertens Res. 2023;46:1132–44.
3. Haze T, Hatakeyama M, Komiya S, Kawano R, Ohki Y, Suzuki S, et al. Association of the ratio of visceral-to-subcutaneous fat volume with renal function among patients with primary aldosteronism. Hypertens Res. 2021;44:1341–51.
4. Neves MF, Cunha AR, Cunha MR, Gismondi RA, Oigman W. The role of renin-angiotensin-aldosterone system and its new components in arterial stiffness and vascular aging. High Blood Press Cardiovasc Prev. 2018;25:137–45.
5. Ohno Y, Sone M, Inagaki N, Yamasaki T, Ogawa O, Takeda Y, et al. Prevalence of cardiovascular disease and its risk factors in primary aldosteronism: a multicenter study in Japan. Hypertension. 2018;71:530–37.
6. Hong N, Kim KJ, Yu MH, Jeong SH, Lee S, Lim JS, et al. Risk of dementia in primary aldosteronism compared with essential hypertension: a nationwide cohort study. Alzheimers Res Ther. 2023;15:136.
7. Haze T, Hirawa N, Yano Y, Tamura K, Kurihara I, Kobayashi H, et al. Association of aldosterone and blood pressure with the risk for cardiovascular events after treatments in primary aldosteronism. Atherosclerosis. 2021;324:84–90.
8. Haze T, Yano Y, Hatano Y, Tamura K, Kurihara I, Kobayashi H, et al. Association of achieved blood pressure after treatment for primary aldosteronism with long-term kidney function. J Hum Hypertens. 2022;36:904–10.
9. Hamanaka G, Ohtomo R, Takase H, Lok J, Arai K. White-matter repair: interaction between oligodendrocytes and the neurovascular unit. Brain Circ. 2018;4:118–23.
10. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. Lancet Neurol. 2019;18:684–96.
11. Bokura H, Saika R, Yamaguchi T, Nagai A, Oguro H, Kobayashi S, et al. Microbleeds are associated with subsequent hemorrhagic and ischemic stroke in healthy elderly individuals. Stroke. 2011;42:1867–71.
12. Lee BC, Tsai HH, Chen ZW, Chang CC, Huang JZ, Chang YY, et al. Aldosteronism is associated with more severe cerebral small vessel disease in hypertensive intracerebral hemorrhage. Hypertens Res. 2023. https://doi.org/10.1038/s41440-023-01458-w.
13. Yuan Y, Li N, Liu Y, Zhu Q, Heizhati M, Zhang W, et al. Positive association between plasma aldosterone concentration and white matter lesions in patients with hypertension. Front Endocrinol (Lausanne). 2021;12:753074. https://doi.org/10.3389/fendo.2021.753074.
14. Dinh QN, Young MJ, Evans MA, Drummond GR, Sobey CG, Chrissobolis S. Aldosterone-induced oxidative stress and inflammation in the brain are mediated by the endothelial cell mineralocorticoid receptor. Brain Res. 2016;1637:146–53.
15. Abbas K, Lu Y, Bavishi S, Mishra N, TomThundyil S, Sawant SA, et al. A simple review of small vessel disease manifestation in the brain, retina, and kidneys. J Clin Med. 2022;11:5546.