Pearls & Oy-sters: Cerebral Microbleeds Caused by Adrenocortical Adenoma-related Primary Aldosteronism

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
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Word count for text: 1415
Character count for the title: 83
Number of references: 9
Number of figures: 1
Number of tables: 0

Search term: All Cerebrovascular disease/Stroke [2], All Clinical Neurology [14], MRI [120], Endocrine [148], Stuttering [301]

Study Funding: This research was supported by a Korea Health Technology R&D Project grant through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health and Welfare, Republic of Korea (grant number HI18C0479), and a National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT; grant number NRF-2019R1F1A1059660).

Disclosure: The authors report no disclosures relevant to the manuscript.
Pearls

- Multiple cerebral microbleeds (CMBs) increase in prevalence with age.

- Hypertension itself is not an independent factor for frequency of CMBs and work up should be performed in patients with age-advanced CMBs.

- Concomitant lobar and deep CMBs are caused by hypertensive small vessel disease rather than cerebral amyloid angiopathy (CAA).

- Primary aldosteronism (PA) can cause numerous concomitant lobar and deep CMBs in a relatively young population through oxidative stress caused by excessive aldosterone and direct injuries resulting from hypertension.

Oysters

- Secondary hypertension should be considered in hypertensive patients with numerous concomitant lobar and deep CMBs and unexplained retinal hemorrhage.

- PA could be among the differential diagnoses in hypertensive patients with concomitant lobar and deep CMBs with accompanying low serum potassium levels.
Case report

A 47-year-old man came to the outpatient neurology clinic at a university-affiliated hospital. He complained of word-finding difficulty and slurred speech, which had occurred abruptly with accompanying dizziness in the morning, 17 days prior to the visit and had been improving since then. He was still working as a computer programmer. His past medical history was significant for hypertension (on 3 antihypertensive medications) over 7 years, a prior episode of transient vertigo with negative work-up and incidental retinal hemorrhages of unclear etiology. At his visit, his blood pressure (BP) was 145 mmHg/95 mmHg. On the National Institute of Health Stroke Scale (NIHSS), he was scored 1 due to mild transcortical motor aphasia. His brain magnetic resonance imaging (MRI) was taken on the same day as appointment and revealed an acute 1.7 cm-sized intracranial hemorrhage (ICH) in the left superior frontal lobe with the ICH score of 0 (Figure, 1A). Furthermore, the MRI showed >200 CMBs in the junctions of the white and gray matter, basal ganglia, pons, and cerebellum on gradient echo (GE) T2-weighted imaging (Figure, 1B). In addition, three lacunes and white matter hyperintensities (Fazekas grade 2) were detected on T2-weighted imaging. He was instructed to keep taking his antihypertensive medications. On the following day, he visited the emergency room with sudden onset right hemiparesis which had occurred at midnight, one hour prior to his visit to the emergency room. His BP was 170/115 mmHg. He was alert and attentive but showed right arm and leg weakness in addition to mild transcortical motor aphasia (3 on NIHSS). His brain CT scan showed a new acute ICH (0 on the ICH score) in the left basal ganglia (Figure, 1C). He was admitted to the ward for conservative management of ICHs. During his admission period for 10 days, his neurologic signs improved with only transcortical motor aphasia remained (1 on NIHSS), but his regimen was up-titrated to include a 4th antihypertensive medication. His blood test revealed
remarkably low levels of serum potassium (3.5 mmol/L on the first day of admission, 3.0 mmol/L on the 4th day of admission, normal range: 3.5-5.1 mmol/L); however, he did not show related symptoms or signs. The NOTCH3 gene test did not detect any pathogenic/likely pathogenic variants. His Apolipoprotein E genotype was ε2/ε3. 18F-flutemetamol amyloid positron emission tomography (PET) was conducted to exclude the possibility of combined CAA. The results revealed no evidence of brain amyloid deposition (Figure, 1D). At his follow-up, 3 weeks after discharge, 24-hour ambulatory BP monitoring showed that his systolic BP was 110-130 mmHg. Therefore, his antihypertensive medications were altered as including three again. Three months after the onset of the second ICH, he returned to his work.

Six months after his ICHs, a follow-up serum electrolyte test revealed low potassium levels (2.7 mmol/L). Therefore, he was recommended to stop taking the diuretic among his antihypertensive medications for one month. However, potassium levels were still low (2.8 mmol/L), then supplemented with oral potassium chloride. And even after discontinuing the diuretic, his BP was 113/83 mmHg. As a result, considering that he presented with numerous CMBs accompanied by two ICHs within an 18-day period, unexplained retinal hemorrhage (Figure, 1E), and persistently low serum potassium, secondary hypertension was suspected. Subsequently, a hormonal test was conducted at 8 am, which revealed the following results (normal range within the parentheses): serum aldosterone 30.31 ng/dl (supine position, 4.1-20.8 ng/dl) and plasma renin activity ≤ 0.20 ng/ml/hr (0.5-1.9 ng/ml/hr). The ratio of serum aldosterone (ng/dl) to plasma renin activity (ng/ml/hr) was over 20, which indicated probable PA and then, a saline loading test, was performed to confirm the PA. After an intravenous injection of 2L of normal saline for 4 hours, serum aldosterone level was 45.87 ng/dl and was not reduced to < 5ng/dl, which confirmed the PA. The adrenal CT (Figure, 1F) showed a 1.7cm-sized mass in the left adrenal gland. Finally, the adrenal mass was removed by
laparoscopic left adrenalectomy, which turned out to be a 1.3x1.3x1.3 cm³, well-defined adrenocortical adenoma (Figure, 1G and 1H). After surgical treatment, his BP was under control with only one antihypertensive medication. In conclusion, he was diagnosed with secondary hypertension due to adrenocortical adenoma-related PA.

Discussion

This case study presents a patient with concomitant lobar and deep CMBs and ICHs caused by adrenocortical adenoma-related PA. Secondary hypertension was suspected because of to the patient presenting with two consecutive ICHs over an 18-day period, numerous CMBs, unexplained retinal hemorrhage, and persistently low serum potassium even after discontinuing his diuretic. Finally, he was diagnosed with adrenocortical adenoma-related PA. The absence of amyloid deposition on his brain PET indicated that the CMBs could be explained by hypertensive small vessel disease due to PA rather than CAA.

Based on the modified Boston criteria, probable CAA is required to have multiple strictly lobar hemorrhages. Because CAA characteristically spares deep structures, any hemorrhagic lesions in basal ganglia, thalamus, or pons exclude the diagnosis of probable CAA.¹ Deep CMBs correlate with MRI findings of hypertensive small vessel disease.¹³ While our patient had multiple cortical CMBs and a recent lobar ICH without any other causes, he was younger than 55 years and also had CMBs/ICH on deep territories. Therefore, his presentation did not satisfy well the criteria for the probable CAA. However, mixed hemorrhagic lesions located in both lobar and deep territories which was shown in our case is another commonly encountered pattern and have posed substantial challenges to clinicians. A recent study demonstrated that mixed-location CMBs are caused by hypertensive small vessel disease rather than CAA.⁴ In addition, amyloid deposition was not revealed in his brain PET.
Therefore, his concomitant lobar and deep CMBs/ICHs were considered to be caused by hypertensive small vessel disease rather than CAA.

A more extensive work-up of secondary causes of hypertension is warranted in patients with sudden onset of hypertension, aggravation of previously controlled hypertension, hypertension onset before age 30, diastolic hypertension with onset after age 65, malignant hypertension, drug-resistant or drug-induced hypertension, unprovoked hypokalemia or excessive target organ damage for hypertension degree. Despite the prevalence of multiple CMBs increasing with age, ≥ 5 CMBs were observed in only 1% of a population in their sixties. Therefore, even in this 47-year old patient with 7-years of hypertension, > 200 mixed-location CMBs was suggestive of disproportionate target organ damage for degree of hypertension and warranted the investigation for secondary hypertension together with his unprovoked hypokalemia.

Owing to the development of the current diagnostic methods, PA is the most common cause of secondary hypertension, with a prevalence rate of 5-15% for patients with hypertension. Furthermore, it can cause cerebrovascular diseases, hypertension, electrolyte imbalance, and cardiovascular changes structurally and functionally. The increased stroke rate in PA may be related to the excessive aldosterone effects on blood vessels and direct damage from hypertension. Aldosterone itself produces oxidative stress, resulting in endothelial dysfunction and collagen remodeling, which causes vessel wall fibrosis. Taking into consideration that the BP of our patient was relatively well-controlled with medication and that hypertension itself is not an independent factor for frequency of CMBs, aldosterone may contribute to the numerous CMBs in our patient. Furthermore, while there have been a few case reports which described CMBs in PA, there were no reports investigating CMBs caused by secondary hypertension due to other causes such as pheochromocytoma. However, future research is warranted to investigate the relationship between CMBs and aldosterone.
itself.

References


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Figure 1. Brain MRI (A and B), brain CT (C), 18F-Flutemetamol amyloid PET scan (D), retinal image (E), adrenal CT (F), adrenal mass specimen (G), and histopathologic section of adrenocortical adenoma (H) in a patient with adrenocortical adenoma-associated with primary aldosteronism.

(A and B) Gradient echo T2-weighted imaging shows an intracerebral hemorrhage (ICH) in the left superior frontal lobe and CMBs in the junction of white matter and gray matter, basal ganglia, and thalami. (C) An acute ICH in the left basal ganglia is seen in the brain CT. (D) 18F-flutemetamol amyloid positron emission tomography (PET) showed no amyloid deposition in his brain. (E) Retinal dotty hemorrhages (arrows) are shown. (F) The adrenal CT (arrow) shows a 1.7 cm-sized mass in the left adrenal gland. (G) The adrenal mass (arrow) is 1.3x1.3x1.3 cm³ in size, and well-defined. (H) Adrenocortical adenoma is pathologically confirmed, based on microscopic findings, well-defined cell borders, polygonal pink cells, clear cells which have abundant, finely vacuolated cytoplasm, and nuclei which are central, round, and bland. (Hematoxylin & Eosin stating, at 400x magnification, bar = 50 μm) CT, computerized tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.
### Appendix 1: Authors

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