



Primary Aldosteronism and Cerebrovascular Diseases

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As diagnostic techniques have advanced, primary aldosteronism (PA) has emerged as the most common cause of secondary hypertension. The excess of aldosterone caused by PA resulted in not only cardiovascular complications, including coronary artery disease, myocardial infarction, arrhythmia, and heart failure, but also cerebrovascular complications, such as stroke and transient ischemic attack. Moreover, PA is associated more closely with these conditions than is essential hypertension. In this review, we present up-to-date findings on the association between PA and cerebrovascular diseases.

Keywords: Primary aldosteronism; Cerebrovascular disorders; Stroke

INTRODUCTION

Primary aldosteronism (PA), which refers to the autonomous excess production of aldosterone, was once considered to be a rare disease. Now, with advances in diagnostic methods, PA has been identified as the most common cause of secondary hypertension [1], with a prevalence ranging from 5% to 15% in hypertension patients [2], and an even higher prevalence in patients with resistant hypertension [3]. Aldosterone excess causes many problems, including hypertension, electrolyte imbalance, and structural and functional cardiovascular changes, and also leads to an increased rate of cerebrovascular diseases. In Asia, a recent Japanese multicenter study in 2018 reported that PA patients had a higher incidence of cardiovascular and cerebrovascular events, including stroke (7.4%), ischemic heart disease (2.1%), and heart failure (0.6%), compared with age-, sex-, and blood pressure-matched essential hypertension (EH) patients [4]. Although the incidence, prevalence, morbidity, and mortality of cerebrovascular diseases have gradually declined, stroke

remains the second leading cause of death throughout the world. Stroke can cause severe and lasting disabilities that require long-term care and rehabilitation programs. Therefore, the global burden of stroke, including the absolute number of patients and those disabled, is still increasing, which poses social and economic problems [5]. In this review, we focus on cerebrovascular diseases in PA patients.

EFFECT OF ALDOSTERONE ON VESSELS

Aldosterone excess damages both the cerebrovascular system and the cardiovascular system. The elevated stroke rate in PA patients may be linked to the effects of aldosterone on vessels. First, hypertension itself, which is a manifestation of PA, is a major risk factor of stroke, and it can cause vessel injury and further remodeling [6]. Hypertension also impairs the blood-brain barrier via endothelial damage caused by the inflammatory response after aldosterone stimulation [7]. Second, the excess of aldosterone is itself a problem, in addition to the direct inju-

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ries caused by hypertension, because aldosterone also generates oxidative stress, which causes endothelial dysfunction and further collagen remodeling, leading to increased fibrosis of vessel walls [8]. Moreover, endothelial inflammation contributes to negative remodeling of the cerebral vasculature, which reduces the vessel diameter, makes the vessel wall less flexible, and further impairs dilatation of the cerebral vessels during cerebral ischemia [9].

In an animal study, oxygen products and nicotinamide adenine dinucleotide phosphate oxidase both increased in rats in which aldosterone was infused [10]. Oxidative stress and inflammation are inhibited by mineralocorticoid receptor antagonists (MRAs), as demonstrated by the reduction of myocardial injury and inflammatory markers, including cyclooxygenase-2 and osteopontin expression, in the treatment group [11]. Aldosterone reduces the bioavailability of nitric oxide and has a direct effect on glucose-6-phosphate dehydrogenase and epidermal growth factor receptor, further increasing vascular stiffness [12]. Moreover, aldosterone causes endothelial progenitor cells to reduce vascular homing, migration, differentiation, and proliferation. Aldosterone also participates in and potentiates the effect of angiotensin II in the extracellular signal-regulated kinase and c-Jun N-terminal kinase signaling pathway to induce fiber formation in vascular smooth muscle cells [13]. Additionally, adaptive immunity may play a role in aldosterone-related vessel injuries. Adoptive T-regulatory lymphocyte transfer in rats prevented inflammation, endothelial dysfunction, and vessel remodeling [14].

VASCULAR CHANGES IN PRIMARY ALDOSTERONISM PATIENTS

It is well documented that aldosterone is responsible for increased arterial wall stiffness, in both morphological or functional aspects [15,16]. Increased stiffness due to aldosterone can be reversed by adrenalectomy [17] or the specific aldosterone antagonist eplerenone [18]. In an animal model, spironolactone prevented aortic fibrosis in spontaneously hypertensive rats, with a slight antihypertensive effect [19]. Increased arterial stiffness is a strong marker of atherosclerosis and a predictor of myocardial infarction [20], as well as a predictor of cerebrovascular diseases [21]. Furthermore, carotid intima media thickness (CIMT) has been found to be related to cardiovascular and cerebrovascular diseases [22]. Increased CIMT was associated with a higher risk of stroke [23].

In our previous study, we demonstrated that patients with al-

dosterone-producing adenoma (APA) had a higher CIMT and an increased brachial-ankle/heart-ankle pulse wave velocity (PWV), suggesting more atherosclerosis and prominent vascular stiffness [24].

ATRIAL FIBRILLATION IN PRIMARY ALDOSTERONISM PATIENTS

Atrial fibrillation (AF) is the most common type of arrhythmia, affecting nearly 1% of the general population. According to the Framingham study, patients with AF had a 5-fold higher risk of stroke than those without AF [25]. Furthermore, approximately 15% to 20% of stroke events are thought to be caused by AF [26].

In 2001, Porodko et al. [27] reported a case that suggested an association between AF and PA. Two other cases in the literature also described AF as a presenting sign of PA [28,29]. In 2005, Milliez et al. [30] found a 12-fold higher risk of AF in PA patients than in EH patients, with age, hypertension duration, and PA as independent predictors. Subsequently, emerging evidence has shown a higher AF rate in PA patients than in EH patients [30-35]. According to the recent meta-analysis by Monticone et al. [36], the odds ratio (OR) of AF in PA patients compared to EH patients was 3.52. We can therefore tentatively assume that the increased rate of stroke in PA patients may be partly attributed to the increased prevalence of AF in PA patients.

CLINICAL STATUS OF CEREBROVASCULAR DISEASES IN PRIMARY ALDOSTERONISM PATIENTS

Previously, genetic and experimental models of hypertension have shown that excess aldosterone caused severe injuries in the heart, brain, and kidneys independently of hypertension itself [37]. Additionally, more and more studies have reported a higher risk of cardiovascular and cerebrovascular disease in PA patients than in EH patients.

In 2005, Milliez et al. [30] reported an increased risk of stroke in 124 PA patients compared with 465 age-, gender-, and blood pressure-matched EH patients (OR, 4.2; 95% confidence interval [CI], 2.0 to 8.6). In 2008, Catena et al. [33] compared cerebrovascular events in 54 PA patients with those in 323 EH patients (with comparable clinical characteristics), and showed a higher rate of stroke or transient ischemic attack (OR, 4.36; 95% CI, 1.49 to 12.8; $P=0.004$) in PA patients. The study also demonstrated benefits from either surgical or medical treatment

in long-term outcomes. Another study by Mulatero et al. [34] in 2013 also showed that a significantly higher percentage of PA patients than EH patients experienced cerebrovascular events (10.4% vs. 4.9%, $P=0.002$) [34].

In 2017, Murata et al. [38] found a significantly higher rate of cerebral infarction in 162 PA patients with excess plasma aldosterone concentrations than in 498 EH patients (9.9% vs. 2.8%; OR, 3.44; 95% CI, 1.54 to 7.74; $P=0.0028$), but such an association was not found in PA patients with normal plasma aldosterone concentrations. The rate of cerebral hemorrhage was also higher in PA patients with excess plasma aldosterone concentrations, but that trend was not statistically significant (3.7% vs. 1.6%; OR, 2.38; 95% CI, 0.74 to 7.22; $P=0.1381$). They found that the increased cerebrovascular risk in PA was related to plasma aldosterone levels. Another study by Monticone et al. [31] also showed that PA patients displayed more cardiovascular events (myocardial infarction, unstable angina requiring angioplasty, stroke, sustained arrhythmias, and heart failure) than EH patients (15.2% vs. 6.0%, $P<0.001$).

One recent study conducted by Hayashi et al. [39] showed that the relative prevalence of cerebrovascular diseases in PA patients was related to the diagnostic method. Cardio-cerebrovascular events were more common in patients with a positive saline infusion test than in those with a negative saline infusion test (12.8% vs. 3.3%, $P=0.04$); while no significant differences were found between patients with positive and negative results of the furosemide upright test and the captopril challenge test [39].

Generally, cerebrovascular events occur in 10% to 20% in PA patients [40]. In 2018, the largest meta-analysis on cardiovascular events in PA patients to date, conducted by Monticone et al. [36], showed that their overall risk of stroke was 2.58 times (95% CI, 1.93 to 3.45) higher than that of EH patients.

EFFECTS OF SURGICAL TREATMENT

In 2018, a large prospective study by Rossi et al. [41] found that surgically treated APA patients had similar AF-free survival to optimally treated EH patients, while a higher risk of AF remained present in medically treated PA patients. Another recent large cohort study by Hundemer et al. [42] demonstrated that surgically treated PA patients showed no statistically significant difference in the risk of developing AF compared with age-matched EH patients. This emphasizes the importance of early recognition of APA patients who may need adrenalectomy to prevent AF.

Furthermore, our Taiwan Primary Aldosteronism Investiga-

tion (TAIPAI) study group also demonstrated that the higher CIMT and increased brachial-ankle/heart-ankle PWV in patients with APA were reversed at 1 year after adrenalectomy [24]. Moreover, baseline vascular condition, hemodynamic factors, and humoral factors including plasma renin activity, plasma aldosterone concentration and serum potassium levels determine the reversibility of arterial stiffness [43]. However, whether these effects can translate into a reduction of stroke incidence requires further study to confirm.

EFFECTS OF MEDICAL TREATMENT

As for medical treatment with MRAs, although Rossi et al. [41] found that a higher risk of AF persisted in medically treated PA patients, Hundemer et al. [44] emphasized the importance of uptitrating the dosage of MRA if renin is suppressed ($<1 \mu\text{g/L/hr}$), indicating insufficient MRA treatment. In their cohort, the baseline incidence of cerebrovascular accidents or transient ischemic attacks was 22 per 1,000 person-years in PA patients, and the adjusted hazard ratio (HR) was 2.38 compared with EH patients (95% CI, 1.83 to 3.08; $P<0.0001$). That study compared the cardiometabolic outcomes between medically treated PA patients and EH patients, and showed a higher incidence of cardiovascular events (myocardial infarction, coronary revascularization, admission for congestive heart failure or stroke) (adjusted HR, 1.91; 95% CI, 1.63 to 2.25) and higher risks for incident mortality (adjusted HR, 1.34; 95% CI, 1.06 to 1.71), diabetes (adjusted HR, 1.26; 95% CI, 1.01 to 1.57), and AF (adjusted HR, 1.93; 95% CI, 1.54 to 2.42) in MRA-treated PA patients than in EH patients. Further analysis showed that the excess risk of cardiovascular events and related mortality was only present in PA patients with suppressed renin. Hundemer et al. [42] also found that the risk of incident AF was similar among MRA-treated PA patients with sufficient mineralocorticoid receptor blockade (renin $\geq 1 \text{ ng/mL/hr}$), PA patients receiving surgical adrenalectomy, and EH patients. However, MRA-treated PA patients with insufficient mineralocorticoid receptor blockade (renin $<1 \text{ ng/mL/hr}$) had a higher risk of developing AF.

OTHER STUDIES RELATED TO CEREbrovascular Diseases IN PRIMARY ALDOSTERONISM PATIENTS

In our TAIPAI database, the incidence of stroke in PA patients was 35 cases per 1,000 person-years [40], much higher than that of the general population (3.4 to 5.2 cases per 1,000 person-

years) [9]. We further found that proteinuria, a medical history of coronary artery disease (OR, 11.12; 95% CI, 3.85 to 33.50; $P < 0.001$) and left ventricular hypertrophy (OR, 3.58; 95% CI, 1.16 to 10.80; $P = 0.023$) were risk factors of ischemic stroke in PA patients [40]. Additionally, Satoh et al. [45] identified the aldosterone-to-renin ratio as a predictor of stroke in subjects with high sodium intake.

The increased stroke rate due to aldosterone excess affects both ischemic stroke and hemorrhagic stroke. In 1988, Litchfield et al. [46] found that patients with glucocorticoid-remediable aldosteronism tended to show an early onset of hemorrhagic stroke and ruptured intracranial aneurysms, which was related to increased aldosterone levels. Mineralocorticoid-induced fibrosis of the cerebral vasculature might predispose patients to vessel rupture.

Another interesting study revealed that the prevalence of PA was 4.0% in acute stroke patients and 4.9% in stroke patients with a history of hypertension [47]. A further analysis showed that female sex, the absence of diabetes, high blood pressure at the initial visit, lower potassium levels, and intracerebral hemorrhage were risk factors for PA. Screening for PA was recommended, especially in patients with characteristics of hyperaldosteronism.

CONCLUSIONS

With the results of these recent trials and meta-analyses, it is clear that PA patients are at an elevated risk for cardiovascular and cerebrovascular morbidity and mortality, including ischemic heart disease, stroke, heart failure, and AF. Most importantly, these complications can be reduced by medical and surgical treatment. These data underscore the necessity of the early recognition and diagnosis of PA, as well as the need for early and appropriate treatment to further decrease the prevalence of cerebrovascular diseases and improve the outcome of PA.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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