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Risk of ischemic stroke in primary aldosteronism patients

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ABSTRACT

Background: High aldosterone concentrations are associated with the risk of stroke that is independent of blood pressure levels. We investigated the risk of ischemic stroke in primary aldosteronism (PA) patients.
Methods: This retrospective case–control study was based on the Taiwan Primary Aldosteronism Investigation (TAIPAI) database from 2004 to 2010. The study group comprised the patients who developed ischemic stroke after the diagnosis of PA. The PA patients who did not develop stroke were matched according to age and sex as the control group. A multivariate logistic regression model was performed to determine the risk factors of ischemic stroke.
Results: Of 339 patients diagnosed with PA, 22 patients (6.5%) developed de novo ischemic stroke. The PA patients with stroke suffered from a longer hypertensive period (11.0 ± 6.5 vs 7.8 ± 8.3, $P = .007$) and a higher prevalence of proteinuria than those who did not develop stroke (40.9% vs 12.9%, $P = .002$). A multivariate logistic regression model showed that PA patients with proteinuria (HR 3.58, $P = .02$), preexisting coronary artery disease (HR 11.12, $P < .001$) or left ventricular hypertrophy (HR 3.09, $P = .047$) were associated with an increased risk of ischemic stroke.
Conclusions: Proteinuria, a medical history of coronary artery disease or left ventricular hypertrophy, was associated with an increased risk of ischemic stroke in PA patients. Our results suggest that a public health initiative is necessary to enhance the follow-up of proteinuria and to manage subsequent stroke among patients with aldosteronism.

1. Introduction

Primary aldosteronism (PA) is among the most common causes of secondary hypertension, accounting for nearly 10% patients referred to specialized clinics [1]. Compared with essential hypertension patients [2], patients with PA are associated with an increased risk of cardiovascular comorbidities, including stroke, myocardial infarction, and atrial fibrillation, which are independent of blood pressure [3,4]. Milliez et al. reported that the rate of stroke was significantly higher in patients with PA than in patients with essential hypertension (12.9% vs 3.4%) [5].

The excess secretion of aldosterone was considered among the pathogenic factors [3]. Elevated plasma aldosterone concentrations are an independent cardiovascular risk factor and contribute to hypertension, a major risk factor for stroke. The incidence of cerebrovascular events (e.g., stroke, aneurysm, and subarachnoid hemorrhage) in patients with glucocorticoid remediable aldosteronism is associated with elevated aldosterone concentrations and suppressed renin activity [6]. A relatively excessive aldosterone concentration (ie, an increased aldosterone-to-renin ratio [ARR]) has been identified as a predictor for stroke or transient ischemic attacks among patients with a normal or high sodium intake [7]. Likewise, experimental models have shown that aldosterone has a pernicious impact on cerebrovascular comorbidity, independent of that of blood pressure [8].

Hypertension causes blood–brain barrier breakdown by triggering mechanisms involving the renin–angiotensin–aldosterone system and that increase endothelial remodeling [9]. The mechanisms underlying blood–brain barrier dysfunction are diverse and may result from endothelial damage caused by oxidative stress as a part of an inflammatory response after aldosterone stimulation [10,11]. Proteinuria, a marker of endothelial dysfunction, increases the risk of stroke by 71%–92% based on rounds of meta-analyses from cohort studies [12], and could also be a prognostic factor of stroke [13].

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2. Material and methods

We conducted a retrospective case–control study based on the Taiwan Primary Aldosteronism Investigation (TAIPAI) database from January 2004 to December 2010. The diagnosis of PA was established in patients with hypertension based on the "modified four corner criteria" previously reported in the supplemental profile [14–16].

2.1. Study population and data retrieval

We identified patients who developed ischemic stroke after diagnosis of PA as study group. Ischemic stroke was defined as a cerebral infarction diagnosed by monitoring focal neurologic signs for more than 24 h and confirmed using brain computed tomographic scans or magnetic resonance imaging (MRI) [17]. Under a case–control design, we analyzed the patients' demographic information, smoking habits, blood pressure, body mass index (BMI), family history of hypertension, and laboratory results, including plasma aldosterone concentration (PAC), plasma renin activity (PRA), serum creatinine aldosterone concentrations, potassium aldosterone concentrations, and urine dipstick tests (for detecting proteinuria). The anti-hypertensive medications at the diagnosis of PA were also recorded.

PRA was measured by the generation of angiotensin I in vitro using a commercially available radioimmunoassay (RIA) kit according to the manufacturer's instructions. The mean (SD) intra-assay and interassay coefficients of variation for the PRA assay were 1.9% (5.0%) and 4.5% (5.2%), respectively. The concentration of PAC was measured by RIA using commercial kits (Aldosterone Maia Kit, Adaltis Italia S.p.A., Bologna, Italy), as previously described [18,19]. Normal PRA levels were between 1 and 5 ng mL^{-1} h^{-1}. The minimal detectable concentration (sensitivity) was 0.018 ng/tube [20]. Using an automatic dipstick analyzer (Aution Max, AX-4030, Arkray Inc.), proteinuria was defined as a protein level reading greater than "trace," whereas the absence of proteinuria yielded a "negative" reading [21]. The patients were asked to assume a supine position, and then blood pressure was measured and recorded using a mercury sphygmomanometer, after a 5-min rest period. The patients' history of hypertension before PA diagnosis was reported by the patients themselves or gathered from medical records. Clinical information including family history and comorbidities, such as diabetes mellitus, coronary artery disease (CAD), hepatitis B, and left ventricular hypertrophy (LVH) were documented. CAD included unstable angina and myocardial infarction, diagnosed by electrocardiogram, cardiac enzymes and cardiac catheterization results. LVH was diagnosed by LV measurement using echocardiography [22]. Patients were censored after receiving an adrenalectomy.

2.2. Statistical analysis

All statistical analyses were performed using the R computer program, ver 2.14.1 (Free Software Foundation). The results were expressed as mean values ± SD. A χ^2 test was performed for analyzing categorical data, and Student's *t* test was used for analyzing continuous data as appropriate. A $p < 0.05$ was considered significant. We conducted a multivariate logistic regression model including variables of age, sex, comorbidities, family history of hypertension, smoking, blood pressure, BMI, PA profiles, proteinuria, eGFR, known duration of hypertension and anti-hypertensive medications to analyze the risk of stroke in PA patients. The goodness of fit (GOF) was assessed using a modified Hosmer–Lemeshow test. The discriminative power of the final model was determined using an area under a receiver operating characteristic (AUROC) curve.

3. Results

Of 346 patients diagnosed with PA, 22 patients (53.8 ± 11.6 y, and 54.5% male) were identified as having had strokes after the diagnosis of PA. Of the PA patients without stroke, 7 patients had some missing data and were excluded for analysis. A total of 317 PA patients who had not had a stroke were identified as the control group. The incidence rate of ischemic stroke was 35 cases per 1000 person-years. Baseline characteristics of the two group patients were shown in Table 1. There were no significant differences in the 2 patient groups regarding age, sex, IHA percentage, cigarette smoking, BMI, or family history of hypertension. However, the stroke patients had a higher prevalence of diabetes (27.3% vs 11.4%, $P = 0.041$), left ventricular hypertrophy (45.5% vs 19.2%, $P = 0.011$), CAD (59.1% vs 7.9%, $P < 0.001$), and proteinuria (40.9% vs 12.9%, $P = 0.002$), than the non-stroke patients did. The blood pressure, serum potassium concentrations, PRA, PAC, and ARR at disease diagnosis were not different between the 2 groups.

The known duration of hypertension before PA diagnosis was longer in the stroke patients compared with the non-stroke group (11.0 ± 6.5 vs 7.8 ± 8.3 y, P = 0.007). Of the anti-hypertensive medications, higher percentage use of calcium channel blockers, beta-blocker and spironolactone were found in the study group. Multivariate logistic regression analysis showed that patients who had proteinuria (HR 3.58, 95% confidence interval [CI] 1.16–10.80), with a history of CAD (HR 11.12, 95% CI 3.85–33.50) or LVH (HR 3.09, 95% CI 0.99–9.49), or use of spironolactone at PA diagnosis (HR 7.08, 95% CI 2.28–21.77) were associated with an increased risk of ischemic stroke (Table 2). The validation test for this model showed an adjusted R^2 of 0.403, and the AUROC value was 0.89.

4. Discussion

Our study showed that PA patients with proteinuria, a history of CAD or LVH, and spironolactone in use at diagnosis are associated with an

Table 1
Demographic characteristics, comorbidities, and clinical features of PA patients who developed ischemic stroke and patients who did not.

	Ischemic stroke ($n = 22$)	Non-stroke ($n = 317$)	*P* value
Patient characteristics			
Male	12 (54.5%)	142 (44.8%)	NS
Age (y)	53.8 ± 11.6	52.2 ± 12.2	NS
Idiopathic hyperplasia (IHA)	8 (36.4%)	178 (56.2%)	NS
Comorbidities			
Diabetes mellitus	6 (27.3%)	36 (11.4%)	0.041
CAD	13 (59.1%)	25 (7.9%)	<0.001
Left ventricular hypertrophy	10 (45.5%)	61 (19.2%)	0.011
Atrial fibrillation	0 (0%)	5 (1.6%)	NS
Family history of hypertension	15 (68.2%)	214 (67.5%)	NS
Smoking	4 (18.2%)	38 (12%)	NS
Systolic blood pressure (mm Hg)	157 ± 26	152 ± 21	NS
Diastolic blood pressure (mm Hg)	97 ± 16	90 ± 13	NS
Mean blood pressure (mm Hg)	117 ± 19	111 ± 14	NS
BMI (kg/m^2)	24.8 ± 4.1	25.6 ± 3.9	NS
Medications			
Calcium channel blocker	22 (100%)	187 (59%)	<0.001
Angiotensin II receptor blocker	11 (50%)	122 (38.5%)	NS
Beta blocker	13 (59.1%)	101 (31.9%)	0.017
Spironolactone	11 (50%)	24 (7.6%)	<0.001
Slow K	0 (0%)	32 (10.1%)	NS
PA profiles			
Aldosterone (ng/dl)	45.2 ± 31.2	51.4 ± 36.3	NS
Plasma renin activity (ng/mL/h)	0.71 ± 1.38	1.10 ± 4.28	NS
Log ARR (ng/dL per ng/mL/h)	2.14 ± 0.64	2.29 ± 0.82	NS
K (mEq/L)	3.45 ± 0.93	3.65 ± 0.73	NS
Creatinine (mg/dL)	1.19 ± 0.46	0.94 ± 0.40	0.006
eGFR ($mL/min/1.73\ m^2$)	68.58 ± 22.23	94.72 ± 36.18	<0.001
Proteinuria [a]	9 (40.9%)	41 (12.9%)	0.002
Known duration of hypertension (y)	11 ± 6.5	7.8 ± 8.3	0.007

Descriptive statistics for categorical variables were expressed as frequency and percentage, while continuous variables were expressed as mean ± standard deviation as appropriate.
ARR, aldosterone renin ratio; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; PA, primary aldosteronism.
[a] A "negative" urine dipstick analysis refers to no proteinuria; "trace to 4+" refers to having proteinuria