Primary Aldosteronism: Factors Associated with Normalization of Blood Pressure after Surgery

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Background: **Hypertension often persists after adrenalectomy for primary aldosteronism.**

Objective: **To determine factors associated with resolution of hypertension after adrenalectomy for primary aldosteronism.**

Design: **Retrospective cohort study.**

Setting: **Tertiary care referral center in Rochester, Minnesota.**

Patients: **All patients who underwent adrenalectomy for primary aldosteronism between 1 January 1993 and 31 December 1999.**

Measurements: **Preoperative plasma renin activity, plasma and urinary aldosterone concentrations, and adrenal imaging. Follow-up blood pressure, measured at a clinic visit or at home, was reviewed.**

Results: **97 adrenalectomies were performed, and follow-up was available in 93 patients. Hypertension was resolved at follow-up (blood pressure < 140/90 mm Hg) without use of antihypertensive agents in 31 of 93 patients (33%). According to a stepwise multivariable logistic regression analysis adjusted for duration of follow-up, resolution of hypertension was independently associated with family history of hypertension in no more than 1 first-degree relative (odds ratio [OR], 10.9; $P < 0.001$) and preoperative use of two or fewer antihypertensive agents (OR, 4.7; $P = 0.005$). Additional factors associated with resolution of hypertension based on univariate analysis included younger age, shorter duration of hypertension, higher preoperative ratio of plasma aldosterone concentration to plasma renin activity, and higher urine aldosterone level ($P < 0.05$).**

Conclusions: **Resolution of hypertension after adrenalectomy for primary aldosteronism is independently associated with a lack of family history of hypertension and preoperative use of two or fewer antihypertensive agents.**

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Primary aldosteronism—a syndrome characterized by hypertension, suppressed plasma renin activity, and excessive secretion of aldosterone—was originally described by Conn in 1955 (1). Although traditional prevalence estimates of primary aldosteronism in the hypertensive population have been 0.05% to 2.2%, recent estimates have been as high as 5% to 13.0% (2–7). Primary aldosteronism may be the most common form of secondary hypertension (4, 8).

Primary aldosteronism is caused by an aldosterone-producing adenoma in 30% to 60% of cases and is considered biochemically correctable with unilateral adrenalectomy (8–16). However, in many cases, hypertension may persist after adrenalectomy. Our primary objective was to determine factors associated with resolution of hypertension after adrenalectomy for primary aldosteronism.

Methods

Patients

A computerized search of surgical procedures, pathologic diagnoses, and dismissal diagnoses was used to identify all patients who underwent adrenalectomy for primary aldosteronism at the Mayo Clinic, Rochester, Minnesota, between 1 January 1993 and 31 December 1999. The complete medical records of all the identified patients were retrospectively reviewed by an endocrinology fellow and a board-certified endocrinologist. The criteria used to establish the diagnosis were a history of hypertension (with or without hypokalemia) with biochemical evidence of hyperaldosteronism and suppressed plasma renin activity (≤ 0.278 ng $\cdot$ L^{-1} $\cdot$ s^{-1} [≤ 1 ng/mL per hour]). Blood pressure had been measured with the patient seated in an ambulatory setting. (If blood pressure was measured in both arms, the higher value was used.) Plasma renin activity and serum and urinary aldosterone concentrations were measured using standard radioimmunoassays in the Mayo Medical Laboratories. Biochemical evidence of hyperaldosteronism was defined as a plasma aldosterone:plasma renin activity ratio of at least 2000 pmol/L per ng $\cdot$ L^{-1} $\cdot$ s^{-1} (≥ 20 ng/dL per ng/mL per hour) with a plasma aldosterone concentration of at least 416 pmol/L (≥ 15 ng/dL) or a urinary aldosterone excretion of 33.2 nmol/d or

Table. **Univariate Analysis of Factors Evaluated for an Association with Resolution of Hypertension**

Characteristic	Resolution of Hypertension		Univariate Analysis	
	Yes (n = 31)	No (n = 62)	Odds Ratio (95% CI)	P Value
Age, *y**	49 ± 15 (22–80)	55 ± 11 (29–73)	1.5† (1.02–2.1)	0.037
Women, *n (%)*	12 (38.7)	19 (30.7)	1.4 (0.6–3.5)	>0.2
Systolic blood pressure, *mm Hg**	154 ± 21 (124–238)	163 ± 22 (120–205)	1.2† (1.0–1.6)	0.07
Diastolic blood pressure, *mm Hg**	98 ± 18 (78–178)	96 ± 11 (75–120)	0.9† (0.6–1.2)	>0.2
Duration of hypertension, *y**	9 ± 8 (<1–30)	13 ± 9 (<1–31)	1.4‡ (1.1–1.9)	0.019
Preoperative treatment with ≤2 antihypertensive agents, *n (%)*	21 (67.7)	22 (35.5)	3.8 (1.5–9.5)	0.004
Family history of hypertension in ≤1 first-degree relative, *n (%)*	27 (87.1)	27 (44.3)	8.5 (2.7–27.3)	<0.001
Preoperative use of potassium supplement, *n (%)*	23 (74.2)	48 (77.4)	0.8 (0.3–2.3)	>0.2
Serum potassium level, *mmol/L**	3.5 ± 0.5 (2.6–4.9)	3.4 ± 0.5 (1.9–4.5)	1.4§ (0.6–3.5)	>0.2
Ratio of plasma aldosterone concentration to plasma renin activity, *pmol/L per ng · L^{-1} · s^{-1}**‖	9370 ± 7130 (1630–31 100)	6400 ± 4990 (1210–27 000)	1.8¶ (1.1–3.0)	0.015
Urinary aldosterone level, *nmol/d**	123 ± 64 (44–321)	100 ± 105 (13–733)	1.9¶ (1.1–3.5)	0.032
Absence of adrenal nodule > 1 cm on computed tomography, *n (%)*	19 (61.3)	32 (51.6)	1.5 (0.6–3.6)	>0.2

* Data for continuously scaled variables are expressed as the mean ± SD (range).
† Odds of having resolution of hypertension per a 10-unit decrease in the value of the variable.
‡ Odds of having resolution of hypertension per a 5-unit decrease in the value of the variable.
§ Odds of having resolution of hypertension per a 1-unit decrease in the value of the variable.
‖ Calculated by dividing the plasma aldosterone concentration by the renin activity value. To convert the ratio of plasma aldosterone concentration to plasma renin activity from pmol/L per ng · L^{-1} · s^{-1} to ng/dL per ng/mL per hour, divide by 99.856.
¶ Odds of having resolution of hypertension per a doubling in the value of the variable.

greater (≥12 μg/24 h) after a 3-day high-salt diet. Before the biochemical variables were measured, drug therapy had not been withdrawn, except for spironolactone, which was withdrawn for at least 1 month. Results on adrenal gland imaging using computed tomography or magnetic resonance imaging were recorded. If adrenal venous sampling was performed, the results were noted. The institutional review board of Mayo Foundation approved the study. Patients provided informed consent for chart review.

Data Collection

We reviewed the patients' complete medical record at Mayo Clinic for all patients who had undergone adrenalectomy and had confirmed primary aldosteronism. Patients lacking postdischarge data in their chart had telephone follow-up. The principal outcome was resolution of hypertension, which was defined as the most recent blood pressure lower than 140/90 mm Hg without the aid of antihypertensive agents.

Statistical Analysis

Each patient characteristic was evaluated for an association with resolution of hypertension on the basis of fitting separate univariate logistic regression models. We performed a stepwise multivariable logistic regression analysis adjusted for duration of follow-up to identify variables independently associated with resolution of hypertension. The α level for inclusion of individual variables was 0.05; however, because many correlated variables were being considered (12 variables), model building ceased if the residual chi-square statistic was insignificant at the 0.10 level. The residual chi-square statistic tested the joint association of the dependent variable with all the variables not in the model at a given step, with adjustment for the number of variables in the model at that step. The strength of the association of each variable with resolution of hypertension was summarized by calculating an odds ratio and a corresponding 95% CI that was calculated from the coefficients estimated in the logistic regression models. Continuous variables that were positively skewed were analyzed on the log-2 scale, and their odds ratios were reported per a doubling in the value of the variable. Statistical analyses were performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Patients

Between 1993 and 1999, 97 patients had adrenalectomy for primary aldosteronism at our institution (**Table**). An adenoma was resected in most patients (89

of 97 [92%]), and the remainder had evidence of adrenocortical hyperplasia without a concurrent adenoma. Follow-up information was available for 93 of the 97 patients (96%), and the median follow-up was 29 months (range, 0.1 to 77.9 months).

Factors Associated with Resolution of Hypertension

Hypertension was resolved (blood pressure $< 140/90$ mm Hg without the aid of antihypertensive agents) in 31 of 93 patients (33%). Of the patients with unresolved hypertension, 61 of 62 (98%) had improved control of hypertension (defined as a decrease in blood pressure or fewer antihypertensive agents taken at follow-up).

According to a stepwise multivariable logistic regression analysis adjusted for duration of follow-up, resolution of hypertension was independently associated with family history of hypertension in one or no first-degree relative (odds ratio, 10.9 [95% CI, 3.0 to 39.0]; $P < 0.001$) and preoperative use of two or fewer antihypertensive agents (odds ratio, 4.7 [CI, 1.6 to 13.9]; $P = 0.005$) ($r^2 = 0.27$). Additional factors significantly associated with resolution of hypertension ($P < 0.05$) according to univariate analysis included younger age, shorter duration of hypertension, higher preoperative ratio of plasma aldosterone to plasma renin activity, and a higher 24-hour urinary aldosterone level (**Table**).

Discussion

In our series, hypertension had resolved at follow-up in approximately one third of patients who underwent adrenalectomy for primary aldosteronism. Resolution of hypertension was independently associated with a lack of a family history of hypertension and preoperative use of two or fewer antihypertensive agents.

Our rate of hypertension resolution after adrenalectomy (33%) was similar to that of another study (35%), in which resolution of hypertension was defined as a blood pressure lower than 140/90 mm Hg and no use of antihypertensive agents at follow-up (17). Other studies have indicated higher rates of resolution of hypertension; however, follow-up blood pressure as high as 160/95 mm Hg were used as the criterion for normotension (12, 16). Our definition of resolution of hypertension is more in line with current treatment goals for hypertension (18).

In our study, resolution of hypertension was associated with a history of hypertension in no more than one first-degree relative and use of two or fewer antihypertensive agents. These variables probably reflect the fact that patients in whom hypertension has resolved do not have concurrent refractory essential hypertension. Similarly, another recent study has shown that having a positive family history of hypertension predicts persistent hypertension after adrenalectomy for primary aldosteronism (16). Other studies have shown that younger age and shorter duration of hypertension can predict resolution of hypertension (11–13, 16, 17, 19). Furthermore, 24-hour urinary aldosterone excretion has been previously shown to predict improvement of hypertension after adrenalectomy for primary aldosteronism (17). In our study, the associations of hypertension resolution with increasing 24-hour urinary aldosterone excretion and increasing ratio of plasma aldosterone concentration to plasma renin activity may reflect a higher preoperative degree of autonomous aldosterone secretion that is corrected after adrenalectomy. Our study may lack the statistical power to show independent associations of these variables with resolution of hypertension.

The main limitation of our study is that our retrospective analysis, with its limited sample size and duration of follow-up, could have recall and referral bias. Another limitation is an unequal duration of follow-up in patients whose hypertension resolved compared with patients whose hypertension did not. Moreover, because increasing duration of follow-up was associated with increasing rates of resolution of hypertension, we may have underestimated the proportion of patients whose hypertension was ultimately resolved after adrenalectomy. We have tried to address the limitation of unequal follow-up by adjusting for this in our multivariable model. The main strength of our study is that it is a relatively large study of a specialized cohort of patients, and this enabled us to perform multivariate analysis of various factors predictive of resolution of hypertension.

In conclusion, unilateral adrenalectomy for aldosterone-producing adenoma resolves hypertension in approximately one third of cases when hypertension is not severe enough to require preoperative use of multiple antihypertensive agents and concurrent essential hypertension is absent. Although prediction of the specific outcome in any particular patient is impossible, clinicians should be aware of variables that are associated

with a lack of blood pressure normalization after adrenalectomy for primary aldosteronism.

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