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Minireview: Primary Aldosteronism—Changing Concepts in Diagnosis and Treatment

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Primary aldosteronism affects 5–13% of patients with hypertension. Patients with hypertension and hypokalemia and most patients with treatment-resistant hypertension should undergo screening for primary aldosteronism with a plasma aldosterone concentration to plasma renin activity ratio. A high plasma aldosterone concentration to plasma renin activity ratio is a positive screening test result, a finding that warrants confirmatory testing. For those patients that want to pursue a surgical cure, the accurate distinction between the subtypes (unilateral *vs.* bilateral adrenal disease) of primary aldosteronism is a critical step. The subtype evaluation may require one or more tests, the first of which is imaging the adrenal glands with computed tomography, followed by selective use of adrenal venous sampling. Because of the deleterious cardiovascular effects of aldosterone, normalization of circulating aldosterone or aldosterone receptor blockade should be part of the management plan for all patients with primary aldosteronism. Unilateral laparoscopic adrenalectomy is an excellent treatment option for patients with unilateral aldosterone-producing adenoma. Bilateral idiopathic hyperaldosteronism should be treated medically. In addition, aldosterone-producing adenoma patients may be treated medically if the medical treatment includes mineralocorticoid receptor blockade. (*Endocrinology* 144: 2208–2213, 2003)

HYPERTENSION, HYPOKALEMIA, suppressed plasma renin activity (PRA), and increased aldosterone excretion characterize the syndrome of primary aldosteronism, which was first described in 1955 (1). Bilateral idiopathic hyperaldosteronism (IHA) and aldosterone- producing adenoma (APA) are the most common subtypes of primary aldosteronism (Table 1). A much less common form, unilateral hyperplasia or primary adrenal hyperplasia, is caused by zona glomerulosa hyperplasia of predominantly one adrenal gland. Two forms of familial hyperaldosteronism (FH) have been described: FH type I and FH type II. FH type I, or glucocorticoid-remediable aldosteronism (GRA), is autosomal dominant in inheritance and associated with variable degrees of hyperaldosteronism, high levels of hybrid steroids (*e.g.* 18-hydroxycortisol and 18-oxocortisol), and suppressibility with exogenous glucocorticoids (2). FH type II refers to the familial occurrence of APA or IHA or both (3).

In this review three questions will be addressed: 1) How common is primary aldosteronism? 2) How should the clinician distinguish between IHA and APA? and 3) What is the best treatment for primary aldosteronism?

How Common is Primary Aldosteronism?

In the past, clinicians would not consider the diagnosis of primary aldosteronism unless the patient presented with spontaneous hypokalemia, and then the diagnostic evaluation would require discontinuing antihypertensive medications for 2 wk. The "spontaneous hypokalemia/no antihypertensive drug" diagnostic approach resulted in predicted primary aldosteronism prevalence rates of less than 0.5% of hypertensive patients (4–9). However, it is now recognized that most patients with primary aldosteronism are not hypokalemic (10–13) and that screening can be completed with a simple blood test [plasma aldosterone concentration (PAC) to PRA ratio] while the patient is taking antihypertensive drugs (except spironolactone; Refs. 13–20). Fifteen prospective studies have been published on the use of the PAC/PRA ratio in screening for primary aldosteronism (12, 14, 19, 21–32). Although there is some uncertainty about test characteristics and lack of standardization (20), the PAC/PRA ratio is widely accepted as the screening test of choice for primary aldosteronism (33–35). It has been suggested that captopril administration may optimize the PAC/PRA test characteristics (10, 36, 37).

Using the PAC/PRA ratio as a screening test followed by aldosterone suppression confirmatory testing has resulted in much higher prevalence estimates (5–13% of all hypertensives) for primary aldosteronism (Table 2 and Refs. 10 and 21–27). The prevalence of primary aldosteronism approaches 20% in patients with resistant hypertension (12). However, the new prevalence data have not yet been uniformly accepted. Although the prevalence studies documented autonomous aldosterone secretion with confirmatory testing (10, 21–32), it has been suggested that the apparent increased prevalence may be a result of misclassifying low-renin hypertension as primary aldosteronism (38, 39).

How common is primary aldosteronism? Although unanimity is lacking among experts, the evidence from almost every continent suggests that primary aldosteronism affects 5–13% of patients with hypertension. Patients with hypertension and hypokalemia, regardless of presumed cause (*e.g.* diuretic treatment), and most patients with treatment-resistant hypertension should undergo screening for primary al-

Abbreviations: APA, Aldosterone-producing adenoma; CT, computed tomography; FH, familial hyperaldosteronism; GRA, glucocorticoid-remediable aldosteronism; IHA, idiopathic hyperaldosteronism; LV, left ventricular; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

TABLE 1. Forms of primary aldosteronism

Aldosterone-producing adenoma (APA)
Bilateral idiopathic hyperplasia (IHA)
Primary (unilateral) adrenal hyperplasia
Aldosterone-producing adrenocortical carcinoma
Familial hyperaldosteronism (FH)
Glucocorticoid-remediable aldosteronism (FH type I)
FH type II (APA or IHA)

TABLE 2. Prevalence of unrecognized primary aldosteronism in patients with hypertension

Author (Ref.)	Country	No. screened	Prevalence
Gordon *et al.* (21)	Australia	199	8.5%
Kumar *et al.* (22)	India	103	8.7%
Kreze *et al.* (23)	Slovakia	115	13.0%
Lim *et al.* (24)	United Kingdom	465	9.2%
Loh *et al.* (25)	Singapore	350	4.6%
Fardella *et al.* (26)	Chile	305	9.5%
Schwartz *et al.* (27)	United States	117	12.0%
Rossi *et al.* (10)	Italy	1,046	6.3%

dosteronism with a PAC/PRA ratio (cutoff is laboratory dependent) with or without captopril administration (Fig. 1). A high PAC/PRA ratio is a positive screening test result, a finding that warrants confirmatory testing.

How Should the Clinician Distinguish between IHA and APA?

Unilateral adrenalectomy in patients with APA or PAH results in normalization of hypokalemia in all; hypertension is improved in all and is cured in approximately 30–60% of these patients (40). In IHA, unilateral or bilateral adrenalectomy seldom corrects the hypertension (41). IHA and GRA should be treated medically. Therefore, for those patients that want to pursue a surgical cure, the accurate distinction between the subtypes of primary aldosteronism is a critical step. The more widespread screening for primary aldosteronism has changed the proportion of patients with APA *vs.* IHA (Fig. 2). From 1957 to 1985, 248 patients (of whom 98% were hypokalemic) were diagnosed with primary aldosteronism at Mayo Clinic, and 68% had either surgically confirmed or probable APA. In 1999 alone, 120 patients (of whom 37% were hypokalemic) were diagnosed with primary aldosteronism at Mayo Clinic, and only 28% had either surgically confirmed or probable APA.

The subtype evaluation may require one or more tests, the first of which is imaging the adrenal glands with computed tomography (CT; Fig. 3). When a solitary unilateral macroadenoma (>1 cm) and normal contralateral adrenal morphology are found on CT in a young patient (<40 yr old) with primary aldosteronism, unilateral adrenalectomy is a reasonable therapeutic option (Fig. 3). However, in many cases, CT may show normal-appearing adrenals, minimal unilateral adrenal limb thickening, unilateral microadenomas (≤1 cm), or bilateral macroadenomas. In these cases, additional testing may be required to determine the source of excess aldosterone secretion. Small APAs may be labeled incorrectly as IHA on the basis of CT findings of bilateral nodularity or normal-appearing adrenals. Also, apparent adrenal microadenomas may represent areas of hyperplasia, and unilateral adrenalectomy would be inappropriate. In addition, nonfunctioning unilateral adrenal macroadenomas are not uncommon, especially in older patients (>40 yr old; Ref. 42).

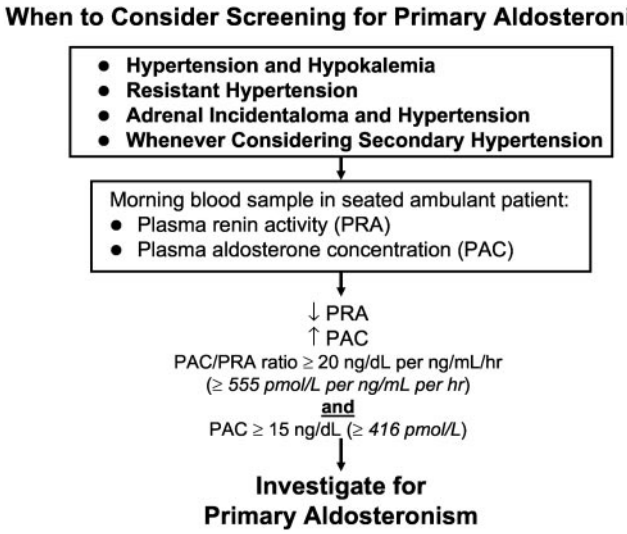

FIG. 1. In patients with suspected primary aldosteronism, screening can be accomplished by measuring a morning (preferably 0800 h) ambulatory paired random PAC and PRA. This test may be performed while the patient is taking antihypertensive medications and without posture stimulation. Spironolactone is the only medication that will absolutely interfere with interpretation of the ratio.

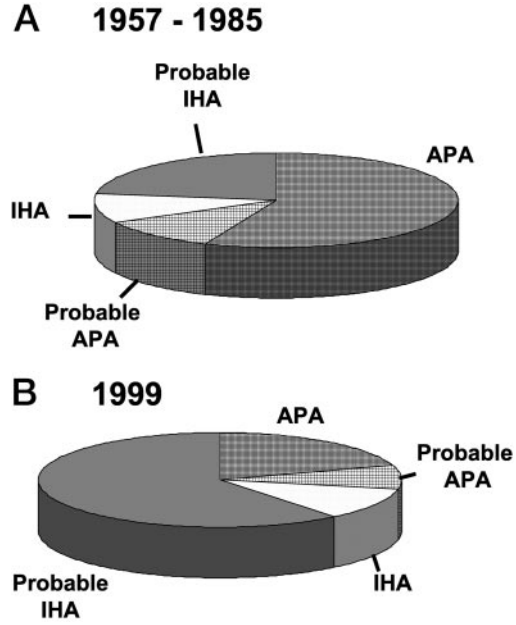

FIG. 2. A, From 1957–1985, 248 patients were diagnosed with primary aldosteronism at Mayo Clinic; 57% had surgically confirmed APA, and 11% had probable APA; the remainder (33%) had probable or confirmed bilateral IHA. B, In 1999, 120 patients were diagnosed with primary aldosteronism at Mayo Clinic; 20% had surgically confirmed APA, and 8% had probable APA; the remainder (72%) had probable or confirmed bilateral IHA.

Patients with APAs have more severe hypertension, more frequent hypokalemia, higher plasma (>25 ng/dl; >694 pmol/liter) and urinary (>30 μg/24 h; >83 nmol/d) levels of aldosterone, and are younger (<50 yr old) than those with

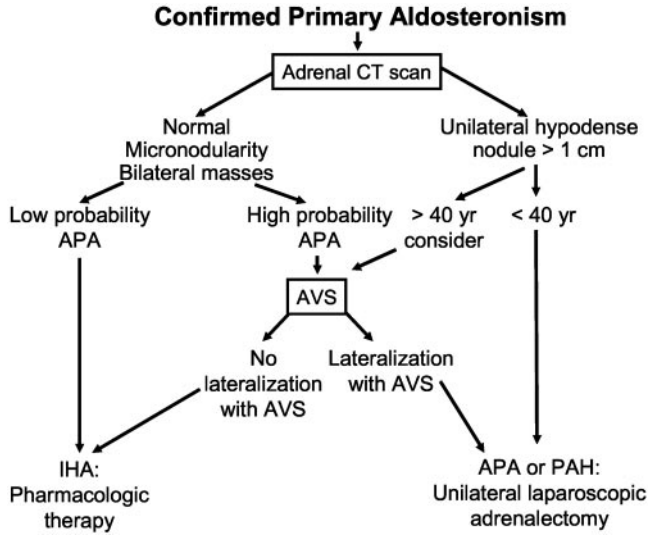

FIG. 3. Subtype evaluation of primary aldosteronism. See text for details. AVS, Adrenal venous sampling; PAH, primary adrenal hyperplasia. [Modified from W. F. Young, Jr., and M. J. Hogan: *Trends Endocrinol Metab* 5:97–106, 1994 (82), with permission from Elsevier.]

IHA (41, 43). Patients fitting these descriptors are considered to have a high probability of APA (Fig. 3). However, these factors are not absolute predictors of unilateral *vs.* bilateral adrenal disease. With the addition of adrenal venous sampling, we have found unilateral APAs in 36% of patients with clinically high-probability APA who had normal findings or unilateral adrenal limb thickening on CT (44). Several studies have found that CT contributed to lateralization in the minority of patients with primary aldosteronism and that adrenal venous sampling is essential to direct appropriate therapy in patients with primary aldosteronism who have a high probability of APA and CT findings of unilateral adrenal limb thickening (34, 45–47).

Adrenal venous sampling is a difficult procedure because the right adrenal vein is small; the success rate depends on the proficiency of the angiographer (45). According to a review of 47 reports, the success rate for cannulating the right adrenal vein in 384 patients was 74% (41). However, with experience, the success rate approximates 90–93% (44, 45). Some centers perform adrenal venous sampling in all patients diagnosed with primary aldosteronism (45). A more practical approach is the selective use of adrenal venous sampling outlined in Fig. 3. Using this approach for the subtype evaluation of 120 primary aldosteronism patients in 1999 at Mayo Clinic, 7% of patients had adrenalectomy based on CT findings alone, and 21% had adrenal venous sampling to guide therapy.

What Is the Best Treatment for Primary Aldosteronism?

The treatment goal is to prevent the morbidity and mortality associated with hypertension, hypokalemia, and cardiovascular damage. The cause of the primary aldosteronism helps to determine the appropriate treatment.

Normalization of Blood Pressure *vs.* Normalization of Aldosterone Levels and/or Its Actions

Normalization of blood pressure should not be the only goal in managing the patient with primary aldosteronism. Mineralocorticoid receptors are present in the heart, brain, and blood vessels, in addition to the kidney and colon. A number of animal studies indicate that aldosterone exerts deleterious effects when plasma concentrations are inappropriate for salt status (48–50). In experimental models of hypertension and heart failure, the nonepithelial effects of aldosterone are mediated via classical mineralocorticoid receptors, and are largely or completely abolished by administration of the aldosterone receptor blocker or by reduction of circulating aldosterone by adrenalectomy (48, 51). It has been demonstrated that selective aldosterone blockade (at doses that do not alter blood pressure) markedly reduces tissue (brain, heart, kidney) damage in saline-drinking spontaneously hypertensive rats (48). Aldosterone induces myocardial fibrosis by either stimulation of cardiac fibroblasts and/or vascular fibrinoid necrosis (52). A clinical correlate of these laboratory studies was the Randomized Aldactone Evaluation Study in which spironolactone produced a 30% reduction in mortality in patients with stage IV congestive heart failure (53, 54). Increased risk of ischemic cardiac events is associated with activation of the renin-angiotensin-aldosterone system (55). Plasminogen activator inhibitor-1 is a major physiologic inhibitor of fibrinolysis (56, 57). Aldosterone increases plasminogen activator inhibitor-1 expression in vascular smooth muscle and endothelial cells (58), and levels correlate with plasma concentrations of aldosterone (59), a correlation inhibited by spironolactone (60).

Patients with primary aldosteronism, when matched for age, blood pressure, and duration of hypertension, have greater left ventricular (LV) mass measurements when compared with patients with other types of hypertension (*e.g.* pheochromocytoma, Cushing's syndrome, and essential hypertension; Ref. 61–63). The LV wall thickness and mass decreased markedly by 1 yr after adrenalectomy for APA, but not in those on medical therapy (64). It should be noted that other studies have been unable to find differences in the degree of LV hypertrophy in patients with primary aldosteronism when compared with patients with renovascular and essential hypertension (65, 66).

The results of studies on small resistance arteries in fat biopsies from patients with primary aldosteronism suggest that there may be some unique vascular remodeling (67, 68). In addition, it has been shown that myocardial damage, when estimated by thallium-201 myocardial scintigraphy, is more severe in patients with primary aldosteronism than in those with essential hypertension—a finding that improves after adrenalectomy (69).

Therefore, normalization of circulating aldosterone or aldosterone receptor blockade should be part of the management plan for all patients with primary aldosteronism.

The Surgical Option

Unilateral laparoscopic adrenalectomy is an excellent treatment option for patients with APA or unilateral hyperplasia. Although blood pressure control improves in nearly

100% of patients postoperatively, average long-term cure rates of hypertension after unilateral adrenalectomy for APA range from 30–60% (40, 70). Persistent hypertension after adrenalectomy is correlated directly with having more than one first-degree relative with hypertension, use of more than two antihypertensive agents preoperatively, older age, increased serum creatinine, and duration of hypertension, and it is most likely due to coexistent primary hypertension (40, 70, 71–73).

Laparoscopic adrenalectomy is the preferred surgical approach and is associated with shorter hospital stays and less long-term morbidity (71, 73). The blood pressure response to spironolactone preoperatively often predicts the blood pressure response to unilateral adrenalectomy in patients with APA. To decrease the surgical risk, hypokalemia should be corrected with spironolactone preoperatively; treatment with this drug should be discontinued postoperatively.

Aldosterone concentrations in blood or urine should be measured shortly after the operation. For the first few weeks postoperatively, a generous sodium diet should be followed to avoid the hyperkalemia of hypoaldosteronism that may occur because of the chronic suppression of the renin-angiotensin-aldosterone axis. Typically, the hypertension resolves in 1–3 months postoperatively. It has been found that adrenalectomy for APA is significantly less expensive than long-term medical therapy alone (74).

The Pharmacologic Option

IHA and GRA should be treated medically (35). In addition, APA patients may be treated medically if the medical treatment includes mineralocorticoid receptor blockade. There have been no placebo-controlled randomized trials evaluating the relative efficacy of drugs in the treatment of primary aldosteronism (75). Spironolactone has been the drug of choice to treat primary aldosteronism for more than three decades. However, it is not selective for the aldosterone receptor. For example, antagonism at the testosterone receptor may result in painful gynecomastia, impotence, and menstrual irregularity. The incidence of gynecomastia in 699 patients treated with spironolactone was dose-dependent (6.9% at doses of $<$50 mg/d and 52% at daily doses of $>$150 mg; Ref. 76). Treatment goals are normotension and normokalemia without potassium supplementation.

Eplerenone is a new steroid-based antimineralocorticoid, which acts as a competitive and selective aldosterone receptor antagonist that has been approved for the treatment of uncomplicated essential hypertension and should be available for use in 2003 (77). The 9,11-epoxide group in eplerenone results in a significant reduction of the progestational and antiandrogenic actions of the molecule compared with spironolactone; eplerenone has 0.1% of the binding affinity to androgen receptors and less than 1% of the binding affinity to progesterone receptors compared with spironolactone (78). The effectiveness of eplerenone in the treatment of mild to moderate essential hypertension in 417 patients has been demonstrated (79). Eplerenone was well tolerated, with the incidence of adverse events similar to placebo. In a separate study, the addition of eplerenone to an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker resulted in significant blood pressure lowering in patients with suboptimally controlled essential hypertension (80). Treatment trials comparing the efficacy of eplerenone *vs.* spironolactone for the treatment of primary aldosteronism have not been published. Presumably eplerenone will be the superior drug if it is shown to be as effective as spironolactone for the treatment of mineralocorticoid-dependent hypertension and if it lacks the limiting antiandrogen side effects of spironolactone.

In patients that are intolerant of aldosterone receptor antagonists, amiloride may be used for its potassium-sparing properties. However, amiloride lacks the mineralocorticoid receptor antagonist benefits. In addition, amiloride is not a very effective antihypertensive agent in patients with primary aldosteronism, and if hypertension persists, a second-step agent (*e.g.* a thiazide diuretic) should be added (81).

Conclusion

The evidence from almost every continent suggests that primary aldosteronism affects 5–13% of patients with hypertension. Patients with hypertension and hypokalemia, regardless of presumed cause (*e.g.* diuretic treatment), and most patients with treatment-resistant hypertension should undergo screening for primary aldosteronism with a PAC/PRA ratio with or without captopril administration. A high PAC/PRA ratio is a positive screening test result, a finding that warrants confirmatory testing. For those patients that want to pursue a surgical cure, the accurate distinction between the subtypes of primary aldosteronism is a critical step. The subtype evaluation may require one or more tests, the first of which is imaging the adrenal glands with CT, followed by selective use of adrenal venous sampling. The treatment goal is to prevent the morbidity and mortality associated with hypertension, hypokalemia, and cardiovascular damage. Because of the deleterious cardiovascular effects of excess aldosterone, normalization of circulating aldosterone or aldosterone receptor blockade should be part of the management plan for all patients with primary aldosteronism. Unilateral laparoscopic adrenalectomy is an excellent treatment option for patients with APA or unilateral hyperplasia. IHA and GRA should be treated medically. In addition, APA patients may be treated medically if the medical treatment includes mineralocorticoid receptor blockade.

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