Clinical Insights

Primary Aldosteronism

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Introduction

Primary aldosteronism (PA) is an endocrine disorder that results from aldosterone overproduction by the adrenal glands, independent of physiological stimuli (hyperkalemia or renin). Symptomatic PA can cause hypertension and hypokalemia, but PA exists across a spectrum of severity from subclinical disease to treatment-resistant hypertension and from normokalemia to severe hypokalemia. PA remains underdiagnosed despite the fact that targeted therapies can reduce morbidity and mortality.[1,2] This Clinical Insights article provides clinicians with a practical approach to diagnosing and managing PA.

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Pathophysiology

The renin-angiotensin-aldosterone system (RAAS) maintains extracellular volume and blood pressure (BP). Normally, low BP stimulates renin release from the kidney, leading to angiotensin II production, which then acts on the adrenal glands to produce aldosterone. Aldosterone activates the mineralocorticoid receptor in the distal nephron, triggering sodium and water reabsorption, increasing blood volume and BP.[3] In PA, aldosterone is overproduced. While PA was historically attributed to aldosterone-secreting masses or bilateral adrenal hyperplasia, evolving data suggest that most cases are likely caused by acquired somatic variants causing aldosterone-producing micronodules with radiologically normal–appearing adrenals.[2]

Epidemiology

The published prevalence of PA has increased in recent years due to more sensitive biochemical assays and the recognition that PA can exist with normokalemia. Prevalence varies with the screened population and selected laboratory cutoff values, but it ranges from 6% in primary care[4] to 29% in patients with treatment-resistant hypertension.[5]

Multiple studies have shown that high-risk patients are rarely screened for PA: only 1% to 2% of patients with PA are diagnosed and treated.[2] Given low screening rates even in high-risk populations, some specialty societies suggest that it is reasonable to screen all patients with hypertension for PA.[5] We recommend particular focus on those with treatment-resistant hypertension and anyone with BP greater than 150/100 mm Hg, adrenal adenoma, hypokalemia, sleep apnea, early-onset hypertension (at younger than 30 years), chronic kidney disease, prepregnancy hypertension, and unexplained atrial fibrillation.[2]

Diagnosis

Screening begins with a seated laboratory measurement of serum potassium, aldosterone, and renin in the morning. As hypokalemia inhibits aldosterone secretion, a patient with hypokalemia may require repeat testing when normokalemic.

The key pathological finding is suppressed renin (plasma renin activity ≤1 ng/mL/h or direct renin concentration of ≤5.2 pg/mL or ≤8.2 mU/L [to convert to picomoles per liter, multiply by 0.0237]) with aldosterone that is not low (≥10 ng/dL or ≥277 pmol/L by immunoassay or ≥7.5 ng/dL or ≥208 pmol/L by mass spectrometry [to convert to microkatals per liter, multiply nanograms per deciliter by 0.0167]) in the setting of normal potassium levels.[6] The aldosterone-to-renin ratio (ARR) has been used as an adjunctive diagnostic test, but there is significant intraindividual variability in ARR, as it compounds the measurement errors of the 2 individual tests, which may lead to underdiagnosis. Thus, clinicians should focus efforts on interpreting the individual renin and aldosterone assays. If testing is negative (unsuppressed renin or low aldosterone with suppressed renin) but the patient has high-risk features detailed previously, repeat testing is warranted.

Table. Pragmatic Approach to Interpreting Laboratory Results for Patients Taking Specific Medications

Medication classes	Effect on testing for PA	Next steps

ACE inhibitors, ARBs, thiazide-like diuretics, SGLT2i, loop diuretics, ENaC inhibitors, MRA	Can falsely raise renin and cause falsely negative ARR	• If renin is low despite these medications, patient likely has PA
		• If renin is not low,
		  • Stop medication for 2 wk (4 wk for MRA) and retest
		  • Temporarily treat empirically with MRA (if switchover to noninterfering medications[a] is unsafe)
		  • Conclude patient does not have PA based on low pretest probability

β-Blockers, clonidine, methyldopa, estrogen-containing OCP,[b] or HRT	Can falsely lower renin and cause falsely positive ARR	• If renin is low, stop medication for 2 wk if safe to do so and retest • If aldosterone is >15 ng/dL by immunoassay or >10 ng/dL by LCMS, unlikely false and ARR caused by β-blocker • If medications cannot be stopped, consider empiric MRA if suspicion is high

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARR, aldosterone-to-renin ratio; ENaC, epithelial sodium channel; HRT, hormone replacement therapy; LCMS, liquid chromatography–mass spectrometry; MRA, mineralocorticoid receptor antagonist; OCP, oral contraceptive pill; PA, primary aldosteronism; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

SI conversion: To convert aldosterone to microkatals per liter, multiply by 0.0167.

[a] Noninterfering medication options: verapamil XR, hydralazine, α-blockers.

[b] Estrogen containing OCP with HRT can falsely lower renin mass but can falsely increase plasma renin activity.

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A common barrier to screening is use of medications that interfere with renin and aldosterone (**Table**). Guidelines suggest initially screening regardless of medications but repeat testing after holding medications if the results are ambiguous.[6] Suppressed renin despite commonly used antihypertensives, such as thiazide-like diuretics or RAAS inhibitors, is strongly suggestive of PA. The role, if any, of aldosterone suppression (previously called confirmatory) tests for PA is uncertain. The first prospective study[7] examining seated saline suppression testing and treatment response to PA-specific treatment as a criterion standard showed high rates of false-negative tests.

A strongly positive screening test should prompt a computed tomography (CT) scan to identify adenomas and lesions at risk for adrenocortical carcinoma. If lesions suggestive of malignant neoplasm are identified (>4 cm or Hounsfield units >10), patients should be referred to an endocrinologist for further evaluation. If there is no concern for malignant neoplasms, the next step is to determine lateralization of aldosterone overproduction with adrenal vein sampling (AVS), particularly if surgery is being considered. This should be undertaken regardless of CT findings, given widespread prevalence of PA in patients with radiologically normal–appearing adrenal glands. AVS is also frequently discordant with visible CT lesions, further emphasizing its utility. However, patients without access to AVS, uninterested in surgery, who are not surgical candidates due to comorbid conditions, or with low likelihood of having lateralizing disease (only mildly positive ARR) do not require AVS and can proceed to medical therapy. Surgery can proceed without AVS for patients younger than 35 years with a unilateral adrenal lesion larger than 1 cm on CT and strongly positive screening tests.

Management

In lateralizing PA (as evidenced by a positive AVS), unilateral adrenalectomy is more effective than medical therapy.[6] Surgical therapy is associated with better BP control and lower rates of stroke, heart failure, and mortality compared with medical therapy with a mineralocorticoid receptor antagonist (MRA).

Despite evidence supporting the benefit of surgery, most patients with PA are treated medically. Medical therapy entails dietary modification with an emphasis on sodium restriction (<2 g sodium/d)[6] and MRA therapy (eg, spironolactone). MRAs should be titrated to normokalemia and normal BP. If tolerated, further up-titration may allow discontinuation of other antihypertensives, simplifying hypertensive regimens and potentially improving outcomes. Titrating MRAs to achieve normal renin has been associated with a lower risk of death, stroke, and atrial fibrillation compared with suppressed renin[8]; however, a causal relationship remains unproven.

Spironolactone is first-line medical therapy given its low cost and broad availability.[6] However, dose-dependent adverse effects (gynecomastia and sexual disturbances) may limit its use, especially in men. Eplerenone has fewer adverse effects and is effective when taken twice daily. There are limited data for the nonsteroidal MRA, finerenone, in patients with PA.[6] Epithelial sodium-channel blockers (amiloride, triamterene) may be used when MRAs are not tolerated.[6] Selective aldosterone synthase inhibitors are under investigation, offering a promising new therapeutic option.[9]

Conclusions

PA presents a huge opportunity to improve the health of our patients, and it is most often treatable with low-cost medications. The first and most important step is screening more patients.

ARTICLE INFORMATION

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