REVIEW CPD

Primary aldosteronism: a common cause of resistant hypertension

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Resistant or difficult-to-control hypertension is a problem that may affect as many as 13% of all persons with hypertension.[1] It is estimated that more than 6 million (22.6%) of adults in Canada have hypertension, but less than two-thirds have it adequately controlled despite conventional strategies for treatment.[2] Uncontrolled hypertension may arise from nonadherence to medication, selection of suboptimal treatment regimens and/or the presence of unidentified secondary causes. It is frustrating for both the patient and treating physician. Patients may embark upon a series of variably successful approaches with different drug classes. We review the accumulating epidemiologic evidence on primary aldosteronism and hypertension that is resistant to treatment. We offer a pragmatic approach to diagnosis for generalist physicians. Although no randomized controlled trials (RCTs) have reported a mortality benefit to screening or treatment for primary aldosteronism, multiple case-control, registry-based and systematic reviews of existing data may be used to construct a coherent, evidence-informed approach to diagnosis and treatment (Box 1). Detection of primary aldosteronism may allow disease-specific treatment that could improve rates of blood pressure control[3] and may reduce the morbidity associated with resistant hypertension.[4]

KEY POINTS

- Difficult-to-control hypertension should trigger testing for primary aldosteronism.
- Measurement of aldosterone-to-renin ratio (ARR) is the preferred diagnostic test.
- Patients with high ARR who are potential candidates for surgical adrenalectomy and those with severe hypertension for whom discontinuation of antihypertensive drugs would be dangerous should be referred to a hypertension specialist for assessment.
- Patients with very severe hypertension who may not tolerate drug adjustment for ARR measures should also be assessed by a hypertension specialist.
- Patients who cannot be considered for adrenalectomy may consider an empiric trial of spironolactone or eplerenone for blood pressure control.
- If a normal or negative result for ARR testing is reported yet clinical suspicion of primary aldosteronism is high, repeating the test is appropriate after the patient has stopped taking all angiotensin-converting-enzyme-inhibitors, angiotensin receptor blockers, dihydropyridine calcium-channel blockers and/or diuretics for at least two weeks, to maximize test sensitivity; use of α-blockers or non-dihydropyridine calcium-channel blockers may be necessary to control blood pressure in the interim.

What is primary aldosteronism?

Primary aldosteronism (called Conn syndrome for many years afterJerome Conn who first described it in 1955[5]) refers to the presence of a benign adrenocortical mass secreting aldosterone in a relatively autonomous fashion, often causing severe hypertension and hypokalemia. In the years that followed the original description, it was quickly recognized that primary inappropriate aldosterone hypersecretion could be due to either an adrenal mass or bilateral hyperplasia of the adrenals.

Aldosterone is a salt-retaining hormone secreted by the zona glomerulosa layer of the adrenal cortex. It is secreted primarily in response to the effect of renin via angiotensin II, although pituitary-derived adrenocorticotropin hormone has a smaller, secondary stimulatory effect, as does an elevated serum potassium concentration. Aldosterone facilitates sodium resorption, and potassium and hydrogen secretion at the principal cells of the distal tubule and collecting duct. Resorption of sodium is considered to be the primary mechanism for an associated rise in blood pressure observed with activation of the mineralocorticoid receptor. Aldosterone also exerts effects on blood vessels, leading to remodelling, fibrosis and endothelial dysfunction, and on the heart, inducing cardiac fibrosis and hypertrophy.

It has been shown that hypokalemia (the traditional clue to the diagnosis of aldosteronism) is only present in less than 20%

Box 1: Evidence used in this review

We searched MEDLINE databases using combinations of the terms "aldosteronism," "resistant hypertension," "refractory hypertension," "prevalence," "review" and "guidelines." This search yielded numerous citations from within the past 15 years. We focused on the most recent publications, systematic reviews, guideline statements and highly cited articles. We focused on articles that included the largest numbers of patients, those that were conducted in a primary care setting and pertinent guidelines (e.g., from the Endocrine Society and Hypertension Canada).

of cases;[6] more likely with an underlying adrenal adenoma as the cause.[7] Very uncommon familial forms of primary aldosteronism may be seen in a pediatric or adolescent patient[8] but most patients present in adulthood.

In primary aldosteronism, there are many potential pathologic processes involved. These include either somatic[9] or germline[10] mutations in the genes for adrenocortical potassium channels, and ectopic hormone receptors.[11] Some recent compelling evidence has suggested that there is a possibility of an independent adipose–cell-secreted ligand that drives aldosterone synthesis and secretion,[12] potentially explaining the link between obesity-related resistant hypertension and aldosterone excess.[13]

How common is primary aldosteronism?

A 2004 review of estimates of prevalence of primary aldosteronism from five continents[14] concluded that primary aldosteronism is more prevalent in modern populations of patients with hypertension than previously thought. Among patient cohorts with resistant hypertension, primary aldosteronism may be present in 10% to 20%,[15,16] and among less-selected populations of patients with mild to moderate hypertension (e.g., as may be typical of primary care) the prevalence is reported at 1% to 6%.[17] A screening study for primary aldosteronism in a primary care environment in Sweden reported a prevalence of 5.5% among 200 patients who were newly diagnosed with hypertension.[18]

As yet, there are no specific geographic or racial markers of increased susceptibility, with broadly similar reports of prevalence for primary aldosteronism now available from countries representing a full spectrum of ethnic diversity.[14,19,20] However, interpretation of these reports is limited by differences in the biochemical definition of primary aldosteronism between centres. A recently published systematic review of studies involving over 42 000 patients concluded that reports of prevalence for primary aldosteronism of 3% to 13% in primary care and 1% to 30% in referral centres were too heterogeneous in nature to allow calculation of a single prevalence point estimate.[21] Nonetheless, the consistent message is that primary aldosteronism is common enough and has sufficiently specific treatment options to justify more frequent diagnostic consideration in primary care (Box 2).

Why is it important to diagnose primary aldosteronism?

Evidence from case–control and registry studies suggests that patients with primary aldosteronism experience higher rates of negative health outcomes than patients with essential hypertension. A case–control study conducted in France that involved 124 patients diagnosed with primary aldosteronism during a three-year period, who were matched for age, gender, and systolic and diastolic blood pressure with 465 patients with essential hypertension, found that patients with primary aldosteronism had increased odds of having a stroke, nonfatal myocardial infarction or atrial fibrillation (for stroke: odds ratio [OR] 4.2, 95% confidence interval [CI] 2.0–8.6; for nonfatal myocardial infarction: OR 6.5, 95% CI 1.5–27.4; for atrial fibrillation: OR 12.1, 95% CI 3.2–45.2).[26] A retrospective study of 270 patients with primary aldosteronism matched 1:3 with 810 patients with essential hypertension and followed for hypertension-related events over 12 years reported a total cardiovascular event rate of 22.6% among the patients with primary aldosteronism compared with 12.7% among those with essential hypertension (OR 2.0, 95% CI 1.4–2.8).[28] A retrospective cross-sectional study involving patients in six centres in Germany reported that cardiovascular complications, in particular, were more common in hypokalemic patients with primary aldosteronism compared with normokalemic patients,[29] which suggests that the presence of hypokalemia in primary aldosteronism may portend a worse prognosis.

Primary aldosteronism appears to be associated with a hyperfiltration renal injury[30] that may not be fully appreciated until after disease-specific therapy is instituted.[31] Smaller studies have also linked primary aldosteronism to a higher risk of left ventricular hypertrophy,[32] enhanced vascular stiffness,[33] vascular dissection,[34] development of type 2 diabetes[35] and poorer quality of life[36] compared with essential hypertension. A study of 3428 patients in a Southern California database reported an 18% prevalence of sleep apnea in patients with primary aldosteronism, significantly higher than a prevalence of 9% in those without primary aldosteronism,[37] suggesting a co-association of two conditions already linked with high risk of cardiovascular disease. Cardiovascular complications in patients with primary aldosteronism occur because effects of inappropriate elevation of circulating aldosterone acting through mineralocorticoid receptors on the heart, blood vessels and kidney.[38,39] The detrimental effect of aldosterone excess (along with high salt intake) appears to lead to vascular smooth muscle prolif-

Box 2: Studies reporting prevalence of primary aldosteronism, determined prospectively, by patient setting* and country

Setting	No. of patients	Country in which study was conducted	Reported prevalence of primary aldosteronism, %
Unselected/primary care hypertension			
Loh K et al.[19]	350	Singapore	5
Fogari et al.[17]	3000	Italy	5.9
Omura et al.[20]	1020	Japan	6.0
Referred to specialty hypertension clinic/resistant hypertension			
Rossi et al.[6]	1125	Italy	11.2
Lim et al.[22]	465	UK	9.2
Abdelhamid et al.[23]	3900	Germany	6.6
Stowasser et al.[24]	300	Australia	18
Yin et al.[25]	313	China	12.5
Milliez et al.[26]	5438	France	2.3†
Matrozova et al.[27]	376	Bulgaria	6.9
Strauch et al.[15]	402	Czech Republic	19

*Minimum of 300 participants.
†Extremely restrictive definition of primary aldosteronism.

eration and fibrosis, along with impaired vascular-endothelial vasodilatory function.[40,41]

Many studies of primary aldosteronism and associated clinical outcomes are potentially confounded by their retrospective design, referral bias and use of surrogate cardiovascular risk markers. However, given that undifferentiated resistant hypertension is already known to be associated with a high degree of morbidity and excess premature death,[42,43] the cumulative evidence of additive health risks of excess aldosterone plus resistant hypertension supports a strong case for early consideration of testing for primary aldosteronism in patients with difficult-to-control hypertension or early cardiovascular complications (Box 3).

How is primary aldosteronism diagnosed?

The hallmark of primary aldosteronism is elevated levels of plasma aldosterone combined with low levels of renin. Normally, the production of renin by the renal juxtaglomerular apparatus leads to the generation of angiotensin I that is then converted to angiotensin II, which eventually stimulates aldosterone synthesis and secretion. When aldosterone is produced autonomously and inappropriately by one or both adrenal glands, normal negative feedback leads to profound suppression of renin. This high-aldosterone/low-renin state is best captured by measuring plasma aldosterone-to-renin ratio (ARR). A high ARR is typically the first clue, especially in the normokalemic patient, to the presence of primary aldosteronism and is currently recommended as the preferred test.[44]

Who should be considered for testing?

The guideline from Hypertension Canada recommends targeted testing for hypertensive patients with features suggestive of primary aldosteronism (Box 4) based on grade-D level evidence (consensus).[46] Testing is particularly useful for patients who would be potential candidates for adrenalectomy if a unilateral adrenal aldosteronoma were to be found. Patients who are already known to be poor surgical candidates may not require extensive investigation. Empiric treatment with mineralocorticoid receptor antagonists (such as spironolactone or eplerenone) may be considered as a preferred alternative.[47,48]

What are the important considerations for ARR testing?

Most patients being screened for primary aldosteronism will already be taking antihypertensive drugs. Debate continues about the exact role and importance of avoiding drug interference in ARR testing.[49,50] At minimum, to avoid false-negative results for the test, patients must refrain from taking spironolactone for at least four to six weeks prior and supplemented with potassium (taken orally) if hypokalemic. Ideally, patients should follow an ad lib or high-salt diet for two days before testing;[51] patients may need specific instruction because many will have been counselled previously to limit sodium intake. Blood samples should be taken with the patient seated and before 10:00 am, although fasting is not required.

Like most endocrine tests, the numeric determination of what constitutes a normal versus abnormal result for an ARR test is often a compromise between acceptable sensitivity and specificity for the disease in question, and any given numerical test cut-off will depend to some extent upon the way the test is reported by an individual laboratory.[45] Box 4 provides suggested ARR interpretation levels that take local laboratory methodology into account, along with an indication of what may be considered a "weakly positive" or "strongly positive" test result. Discussion with the local laboratory director may be necessary to determine which line will be most applicable to the practitioner's setting. If a "normal or negative" result for ARR testing is reported yet clinical suspicion of primary aldosteronism is high, repeating the test is appropriate after the patient has stopped taking all angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium-channel blockers and/or diuretics for at least two weeks, to maximize the sensitivity of the test.[44] Prescription of α-blockers or non-dihydropyridine calcium-channel blockers may be necessary to control blood pressure in the interim.

What should be done for patients with a high result for ARR testing?

After a positive ARR test result, biochemical confirmatory testing is frequently recommended;[44] consultation with an expert in hypertension should be considered because confirmatory testing can be challenging to perform and difficult to interpret. However, confirmatory testing may be unnecessary for highly probable cases, such as those with spontaneous hypokalemia or extremely elevated ARRs,[52,53] which are features strongly predictive of aldosterone-producing adrenal adenoma.[7] Proceeding with further localization investigations should be guided by patient preference, feasibility of surgery and availability of specialized endocrine testing facilities once there is biochemical confirmatory testing of primary aldosteronism. In patients with unilateral adrenal disease, adrenalectomy may be curative. In patients unwilling or unable to undergo surgery, or those with bilateral adrenal hyperplasia, empiric therapy with an aldosterone antagonist such as spironolactone or eplerenone should be considered.

Box 3: Increased risk of complications associated with primary aldosteronism compared with essential hypertension

- Stroke[26]
- Nonfatal myocardial infarction[26]
- Atrial fibrillation[26]
- Albuminuria[30]
- Chronic kidney disease[30]
- Left ventricular hypertrophy[32]
- Vascular stiffness, dissection[33,34]
- Metabolic syndrome/type 2 diabetes[35]
- Obstructive sleep apnea[37]
- Anxiety/depression[36]

Spironolactone has been in clinical use for over 50 years and is a potent blocker of the mineralocorticoid receptor. As an older drug, it has never been studied in a large prospective controlled trial for essential hypertension, but clinical experience has shown repeatedly that this agent is highly effective at controlling blood pressure in those with primary aldosteronism,[54] elevated ARR[48,55] and resistant hypertension.[45] It is inexpensive and widely available. Antiandrogen activity leading to symptoms such as gynecomastia occurs in as many as 10% of older men who are taking 25 mg per day,[56] with higher rates at larger dosages. As an antiandrogen, it should not be offered to women of child-bearing age without contraception. After starting spironolactone therapy, monitoring of serum creatinine and electrolyte levels is suggested to watch for hyperkalemia, particularly in those patients with renal impairment (estimated glomerular filtration rate of < 40 mL/min/m^2)[57] or those who are taking other drugs that predispose to hyperkalemia, such as ACE inhibitors or angiotensin receptor blockers.[58] Eplerenone is newer and has much less propensity to block the androgen receptor and thus cause less gynecomastia;[59] however, it is more expensive than spironolactone at present and less potent.

As many as 97% of patients with primary aldosteronism may achieve blood pressure control following either surgery or targeted medical treatment,[60] and evidence from two small prospective studies suggests equal efficacy in the prevention or regression of complications from primary aldosteronism.[61,62] A meta-analysis of studies involving patients undergoing adrenalectomy that examined surgical outcomes for primary aldosteronism reported that 52% (95% CI 44%–60%) of these patients (n = 1685) were able to achieve drug-free normotension.[3] Further prospective studies are needed to determine whether surgical (removing aldosterone excess) or medical treatment (blocking aldosterone excess) is superior for ameliorating the hypertensive and tissue consequences of this disease.

What is the role of primary care in case finding for primary aldosteronism?

Primary aldosteronism has been shown to be a serious and common cause of resistant hypertension worldwide. A diagnosis of primary aldosteronism frequently follows a lengthy history of hypertension. Prospective studies involving patients undergoing treatment for primary aldosteronism have indicated that many patients with primary aldosteronism have substantial chronic renal injury that is uncovered by treatment following diagnosis, which appears to be irreversible even after correction of primary aldosteronism.[31,63] This evidence points to an important role for primary care practitioners to become more involved in the selection of patients for primary aldosteronism testing in conducting the initial diagnostic test. Randomized controlled trials of screening for primary aldosteronism versus no screening are unlikely to be conducted; therefore, recommendations for practical incorporation of diagnostics for primary aldosteronism in routine care are needed now. Some clinical questions remain (see Box 5). However, for now, recognition of a diagnosis of primary aldosteronism will allow physicians to "put a name" on many difficult-to-treat cases of resistant hypertension and will pave the way for individualized disease-specific treatment.

Conclusion

Primary aldosteronism is now known to be a relatively common cause of resistant hypertension worldwide. Beyond its relation with uncontrolled blood pressure, it may play a tissue-specific

Box 4: Approach to investigating suspected primary aldosteronism

Indications for testing for primary aldosteronism recommended by Hypertension Canada[46]

- Uncontrolled hypertension (> 140/90 mm Hg) despite use of three drugs, one of which is a thiazide/thiazide-like diuretic
- Hypertension with hypokalemia induced by use of thiazide/thiazide-like diuretics (< 3.0 mmol/L)
- Spontaneous hypokalemia with hypertension (< 3.5 mmol/L)
- Hypertension with known adrenal mass

How to request testing for aldosterone-to-renin ratio[45]

- Patient should stop taking spironolactone or eplerenone for four to six weeks prior to testing.
- Patient should be instructed to follow a high-salt diet for two days prior to testing.
- If hypokalemic, the patient should receive oral potassium replacement to restore eukalemia.
- Plasma levels of aldosterone and renin should be requested, with sample collection occurring while the patient is seated and prior to 10:00 am (fasting is not required).

Interpretation of aldosterone-to-renin ratio*[44]

Method for measuring renin	Weak positive result for ARR	Strong positive result for ARR
Plasma renin activity (ng/mL/h)	550–750	> 750
Renin concentration (mU/L)	60–90	> 90
Renin concentration (ng/L)	100–144	> 144

Note: ARR = aldosterone-to-renin ratio.
*Dependent upon the method for renin measurement used by the local laboratory; however, standard reporting of aldosterone in pmol/L is assumed.

Box 5: Unanswered questions

- Does more aggressive or standardized screening for primary aldosteronim improve rates of blood pressure control among patients with resistant hypertension?
- What is the most cost-effective approach to the investigation of primary aldosteronism in Canada?
- What other clinical scenarios warrant consideration of a diagnosis of primary aldosteronism (e.g., obstructive sleep apnea)?
- Does a strategy of aldosterone antagonism improve morbidity or mortality in hypertensive patients compared with present treatments?

role in the adverse cardiovascular consequences that accompany resistant hypertension. For patients with a diagnosis of primary aldosteronism, disease-specific treatment is widely available, inexpensive and effective for control of blood pressure. Measurement of ARR for diagnosis of primary aldosteronism can be readily implemented and is a highly useful tool in primary and specialty care to facilitate the detection, diagnosis and treatment of this potentially remediable condition.

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