Primary aldosteronism

Efficiently making a commonly missed diagnosis

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Primary aldosteronism is a highly prevalent but underdiagnosed cause of hypertension despite targeted therapies being readily available. Increased awareness of this condition will improve rates of diagnosis and outcomes for affected individuals.

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What is primary aldosteronism and how common is it?

Primary aldosteronism (PA), also known as Conn syndrome, is a common cause of secondary hypertension characterised by autonomous aldosterone production with suppressed plasma renin concentration. In normal physiology, aldosterone is produced in response to sodium and volume depletion, which stimulates the production of renin and subsequently angiotensin II. Aldosterone production is also stimulated by a high potassium level. However, in PA, aldosterone production is autonomous and at least partly independent of renin and potassium, hence the renin concentration is usually suppressed and the serum potassium level may be low.[1]

Key points

- **Primary aldosteronism (PA), characterised by autonomous aldosterone secretion from the adrenal glands, is a common but underdiagnosed form of hypertension.**
- **PA causes an increased risk of heart disease, stroke and atrial fibrillation compared with blood pressure-matched essential hypertension.**
- **The clinical features of PA can vary from asymptomatic hypertension to resistant hypertension, with hypokalaemia being present in a minority of patients.**
- **Screening for PA is performed with the plasma aldosterone concentration (within or above normal range), renin level (direct renin concentration or plasma renin activity that is low or suppressed) and the calculated aldosterone-to-renin ratio (raised above a laboratory-specific threshold).**
- **A positive screening test is followed by confirmatory testing, and then subtyping with adrenal imaging and adrenal vein sampling to determine if the aldosterone excess is from one adrenal gland (unilateral PA) or both (bilateral PA).**
- **Unilateral PA can be cured with laparoscopic adrenalectomy, whereas bilateral PA can be treated effectively with mineralocorticoid receptor antagonists such as spironolactone.**

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PA has a reported prevalence of 4 to 14% in patients with hypertension in the primary care setting, 12 to 19% in individuals with stage 3 hypertension, and 20 to 29% in individuals with resistant hypertension.[2-8] Of note, a recent Australian study found a prevalence of 14% in treatment-naïve individuals with hypertension.[3] Despite the high prevalence reported in study populations, PA is rarely screened for, as shown by recent studies evaluating PA screening rates. Among 4660 US adults with resistant hypertension, only 2.1% had received a screening test within two years of meeting criteria for resistant hypertension, whereas a separate study showed that only 1.6% of 269,010 US veterans with treatment-resistant hypertension had been tested for PA.[9,10] The rate of screening was even lower, at 0.7%, in a population-based cohort study in Canada of 1.1 million adults with hypertension.[11]

Why does this matter in general practice?

Hypertension accounts for 5.8% of the total burden of disease in Australia, according to most recently published government data, and general practice is the frontline of hypertension management.[12] GPs are therefore best placed to assess for PA in patients with newly diagnosed hypertension. Screening for PA is straightforward when performed in treatment-naïve individuals with newly diagnosed hypertension but can become complicated subsequently because most commonly used antihypertensive therapies can cause false-negative or false-positive screening test results.[13]

How do patients with PA present?

Individuals with PA present variably. An affected individual may be completely asymptomatic or may present with symptomatic hypertension or hypokalaemia. Possible symptoms include headaches, dizziness and visual changes due to severe hypertension, or muscle cramps, weakness, polyuria and palpitations due to hypokalaemia. Longstanding undiagnosed PA may result in presentation with sequelae of cardiovascular, cerebrovascular and renal complications, including renal impairment, arrhythmia, stroke, ischaemic heart disease or cardiac failure.

Hypokalaemia was thought to be a cardinal feature of PA; however, a range of prevalence studies have identified its presence in only 10 to 30% of individuals with confirmed PA.[2,6,14] The presence of spontaneous hypokalaemia would support clinical suspicion of PA; however, its absence should not preclude further testing. The lack of specific clinical features in patients with PA may contribute to mislabelling of PA as essential hypertension.[15,16] Awareness of the clinical spectrum of PA is key to ensuring it is not overlooked in the assessment of an individual with hypertension.

Why is it important to make the diagnosis?

Making an accurate diagnosis of PA is important, as individuals with PA have a two- to fourfold increased risk of adverse cardiovascular and renal outcomes, including coronary artery disease, heart failure, stroke, atrial fibrillation and proteinuria, compared with blood pressure-matched counterparts with essential hypertension.[17,18] Aldosterone excess has been associated with endothelial dysfunction, myocardial inflammation and increased myocardial collagen deposition, all of which contribute to an increased rate of cardiovascular events in PA.[19-22] Renal sequelae include relative kidney hyperfiltration beyond the effect of hypertension, which may mask underlying renal disease by increasing the estimated glomerular filtration rate to within the normal range.[23,24] Metabolic complications of PA have also been described, including impaired insulin sensitivity and nonalcoholic fatty liver disease.[25,26] The timely and accurate diagnosis of PA allows for the prospect of curing hypertension or prescribing targeted pharmacotherapy, both of which will minimise the risk of multisystem and end-organ damage resulting from excess aldosterone secretion and prolonged hypertension.

To enable targeted treatment, the cause of PA must be identified. The most common causes of PA are an aldosterone-producing adenoma or adrenal hyperplasia, with the former typically being unilateral and the latter bilateral.[16] Rare causes of PA include familial hyperaldosteronism (e.g. glucocorticoid-remediable hyperaldosteronism), unilateral hyperplasia and adrenocortical carcinoma. An aldosterone-producing adenoma or unilateral hyperplasia is ideally managed with surgical resection, whereas bilateral causes of PA are treated with mineralocorticoid-receptor antagonists (MRA) such as spironolactone.[27]

What is the process of working up and diagnosing PA?

The diagnosis of PA involves a screening test followed by a confirmatory test, and, if positive, subtyping to determine if the source of aldosterone excess is unilateral or bilateral (Flowchart).[27,28]

Current Endocrine Society guidelines suggest that PA testing should be undertaken in individuals with:

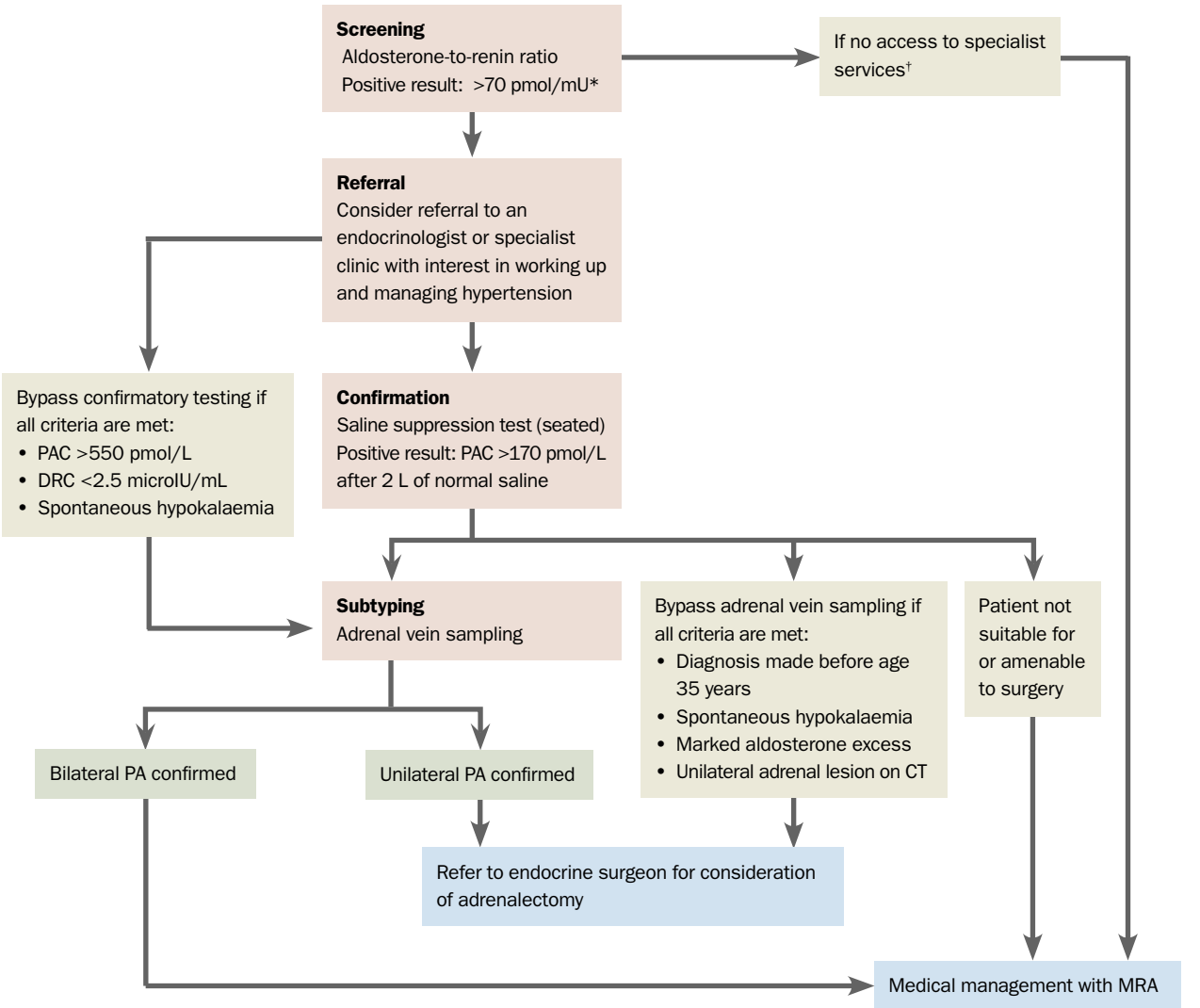
- hypertension who have a family history of early-onset hypertension or stroke before the age of 40 years
- a first-degree relative with PA
- hypertension that is greater than 150/100 mmHg, drug resistant, accompanied by hypokalaemia or present in the context of an adrenal adenoma or sleep apnoea.[27]

Emerging evidence suggests that for a more timely diagnosis, PA testing should be done shortly after the detection of hypertension before the initiation of antihypertensives.[3,29]

Screening tests

The aldosterone-to-renin ratio (ARR) is the most widely used screening test for PA. Multiple factors affect the ARR, with the major one being interfering medications (Table).[27,30] A false-negative ARR can be caused by diuretics (including MRA), ACE inhibitors, angiotensin-receptor blockers and dihydropyridine calcium channel blockers due to their stimulation of renin production. An ARR that is low in the presence of medications that cause a false-negative result does not exclude PA; however, an ARR that is positive in this same context is significant and should prompt further testing. Conversely, beta blockers and centrally acting alpha-2-agonists can result in a

Clinical pathway for screening, confirming, subtyping and managing primary aldosteronism[27,28]



Abbreviations: CT = computed tomography; DRC = direct renin concentration; MRA = mineralocorticoid-receptor antagonist; PA = primary aldosteronism; PAC = plasma aldosterone concentration.

* Using aldosterone concentration (pmol/L) and direct renin concentration (mU/L).

† This is not the ideal pathway but an option if unable to access specialist services or patient declines further investigation.

false-positive ARR by lowering renin. To optimise the accuracy of the ARR, interfering medications should be withheld and non-interfering antihypertensive agents introduced four to six weeks before performing the ARR. Noninterfering options include verapamil, hydralazine, moxonidine and prazosin. Blood pressure can be monitored by the patient at home or by the GP at least once a week, to enable gradual uptitration of these alternative antihypertensive medications to maintain blood pressure less than 140/90 mmHg during the investigative period.

The oral contraceptive pill, hormone replacement therapy and NSAIDs can also interfere with the ARR, but it is not always feasible to withdraw hormonal therapy. It is therefore important to note the presence of these agents when interpreting the ARR. In most Australian laboratories, the threshold for an abnormal ARR, when plasma aldosterone concentration (pmol/L) and direct renin concentration (mU/L) are both measured by immunoassays, is greater than 70 pmol/mU. Renin may also be measured as plasma renin activity, which has a different reference range. In premenopausal women the ARR should be assessed in the follicular phase of the menstrual cycle as aldosterone levels rise in the luteal phase.[31] The

Table. Common causes of false-positive and false-negative screening test results for PA*

	Causes of false-positive aldosterone-to-renin ratio	Causes of false-negative aldosterone-to-renin ratio
Drugs	• Beta blockers • Central agonists including clonidine and methyldopa • NSAIDs • Oral contraceptive pill (if direct renin concentration measured)	• Angiotensin-receptor blockers • ACE inhibitors • Mineralocorticoid receptor antagonists • Dihydropyridine calcium-channel blockers • Loop diuretics • Thiazide diuretics
Conditions	• Potassium over-replacement or loading • High salt intake • Menstrual cycle: blood taken during the luteal phase (if direct renin concentration measured; plasma renin activity unaffected) • Renal impairment	• Hypokalaemia • Salt restriction • Pregnancy • Malignant hypertension • Renovascular hypertension

Abbreviation: PA = primary aldosteronism.
*Adapted from Funder J, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline.[27]

risk of a false-positive ARR in the context of oral contraceptive pill use is present when direct renin concentration is measured but mitigated by measuring plasma renin activity.[32]

It is also important to correct hypokalaemia and advise liberal salt intake to avoid false-negative ARR results.[27] A summary of strategies to prepare the patient for their ARR test is provided in the Box. The ARR should ideally be measured more than once, due to significant intraindividual variability, before discounting the possibility of PA or proceeding to confirmatory testing.[33]

Confirmation tests

The objective of a confirmation test is to assess for autonomous aldosterone secretion that is unresponsive to physiologically inhibitory stimuli. There are multiple options, including the seated saline suppression test, oral salt loading, the fludrocortisone suppression test and captopril challenge test.

Summary of strategies to prepare patients for the ARR screening blood test for PA

- Correct hypokalaemia with oral potassium supplements and aim for a potassium level greater than 4 mmol/L
- If safe to do so, stop diuretics (hydrochlorothiazide, mineralocorticoid receptor antagonists) for 6 weeks before the test
- If safe to do so, stop ACE inhibitors, angiotensin-receptor blockers, beta blockers, alpha-2-agonists and NSAIDs for 4 weeks before the test
- If possible, stop the oral contraceptive pill and use alternative contraception, otherwise consider hormonal interference during result interpretation
- Perform the blood test in the morning, about 2 hours after the patient has arisen from bed

Abbreviations: ARR = aldosterone-to-renin ratio; PA = primary aldosteronism.

The seated saline suppression test is used often, as it is a day procedure and uses saline solution rather than drug therapy; however, a saline load does pose the risk of fluid overload in people with renal or cardiac insufficiency.[34] A positive seated saline suppression test is defined by an aldosterone concentration greater than 170 pmol/L (as measured by immunoassay) after the administration of 2 litres of normal saline, with an aldosterone concentration of 171 to 217 pmol/L considered the grey zone.[35]

Confirmatory testing can be bypassed if an individual has an aldosterone concentration above 550 pmol/L and a direct renin concentration below 2.5 microIU/mL with spontaneous hypokalaemia.[28]

Subtyping

After confirmation of autonomous aldosterone secretion, the next step is to subtype the source of aldosterone excess as unilateral or bilateral. Adrenal computed tomography (CT) imaging is performed in all patients with confirmed PA to evaluate for an adrenal tumour.[27] The result is not sufficient to subtype PA, as an incidental nonfunctioning adrenal tumour may be present in the context of bilateral adrenal hyperplasia, or a functioning small adenoma may escape detection with adrenal imaging.[36]

Adrenal vein sampling (AVS) is considered the gold standard for subtyping. Multiple studies identifying discordant results between imaging alone and AVS reinforce that a definitive subtype is best achieved by AVS.[37-39] AVS is, however, invasive, technically challenging and costly. It is therefore worthwhile referring patients to a tertiary centre with specialised expertise in AVS. An individual should only undergo AVS if amenable to and suitable for surgical management. Alternatives to AVS such as NP-59 scintigraphy have been explored but are not used in routine practice.

The Endocrine Society guidelines advise that AVS can be bypassed in a young patient (under 35 years of age) with spontaneous hypokalaemia, marked aldosterone excess and a unilateral adrenal lesion on CT, who can proceed directly to unilateral adrenalectomy.[27]

Management and follow up

If unilateral PA is confirmed on AVS (or the criteria to bypass AVS are met), referral to an endocrine surgeon for consideration of laparoscopic adrenalectomy is the next step. If adrenalectomy is not appropriate or acceptable to the individual with confirmed PA, medical management with MRA therapy should be pursued.

MRA therapy is prescribed with the goal of achieving normotension and normalising the plasma renin concentration for optimal cardiovascular risk minimisation.[40] The patient should be assessed for serum potassium levels and adverse effects. Spironolactone is the first-line MRA therapy, with a starting dose of 12.5 to 25 mg daily. This can then be uptitrated every four to eight weeks to a dose of 100 mg daily if required. Adverse effects such as gynaecomastia and mastodynia (in men) and menstrual disturbance (in premenopausal women) are more common at doses above 50 mg per day, due to the antiandrogenic and prostagenic effects of spironolactone.[41] Eplerenone is an alternative MRA if spironolactone is not tolerated; however, it is less potent, requires twice-daily dosing and is not subsidised in Australia by the PBS for the treatment of hypertension.[42] It can be commenced at a dose of 25 mg daily.

Where there is suspicion that an individual may have PA, a referral to a specialist clinic or endocrinologist can be made to facilitate screening, confirmatory testing and/or AVS. Ongoing follow up in the general practice or specialist clinic should involve blood pressure monitoring, evaluation of aldosterone, renin and electrolyte levels and screening for cardiovascular, renal and metabolic comorbidities.

Conclusion

PA is a common disease and should be considered in any individual with hypertension, given the lack of specific symptoms and signs. The diagnosis of PA involves screening with an ARR, confirmatory testing (often with the seated saline suppression test) and subtyping (the gold standard being AVS). Aldosterone excess has deleterious effects extending beyond the impact of hypertension, with possible complications including cardiovascular disease and renal impairment. Therefore, timely diagnosis and treatment is important to prevent these complications or mitigate their consequences. Referral of patients with PA to an endocrinologist and/or an endocrine surgeon as part of the multidisciplinary team is likely to be beneficial for targeted treatment and long-term management. **ET**

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A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

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