Primary aldosteronism

Making the diagnosis and why it matters

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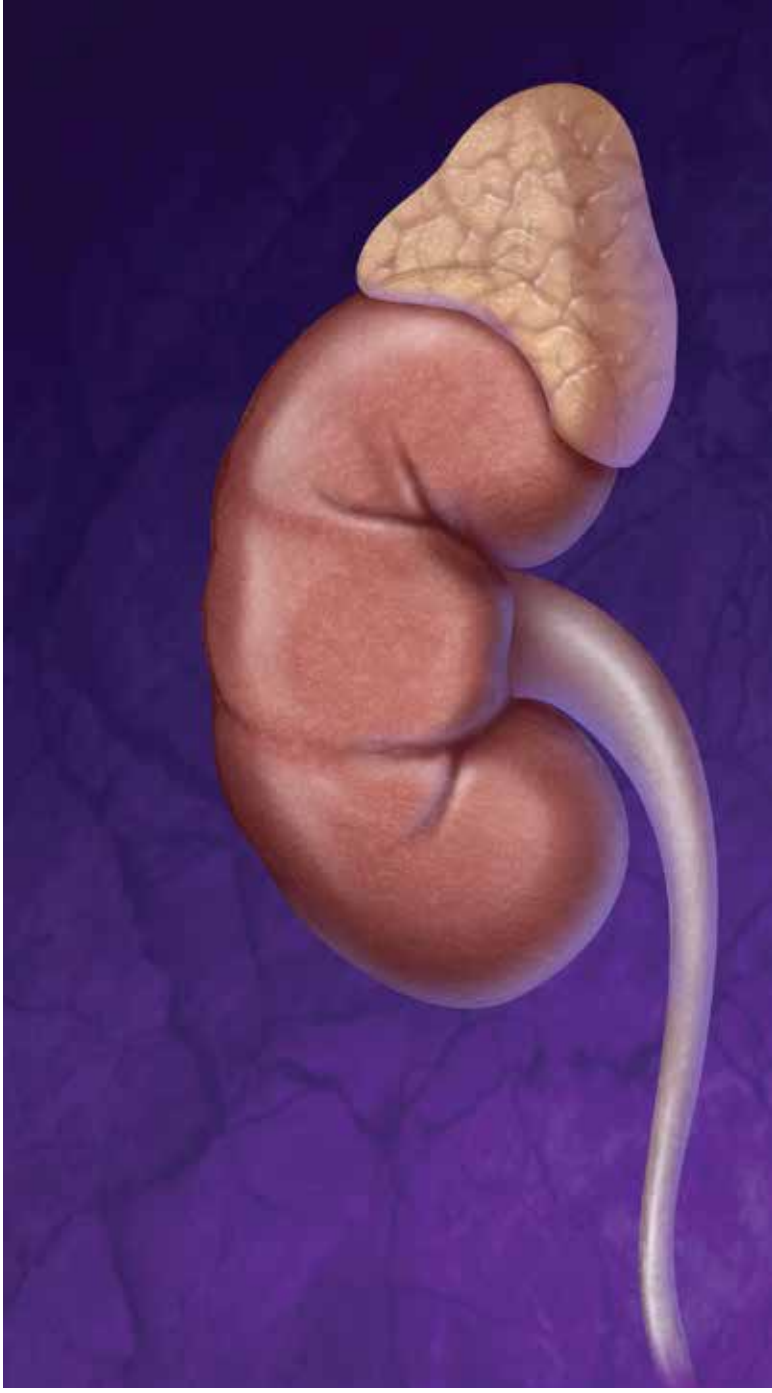
It has been recognised that primary aldosteronism is a much more common cause of hypertension than previously thought and this has led to increased interest in this condition. Being a common but potentially reversible cause of cardiovascular morbidity and reduced quality of life, primary aldosteronism is well worth looking for.



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In patients with primary aldosteronism, a condition first described by Jerome Conn in 1954, more of the salt-retaining hormone aldosterone is produced by the adrenal cortex than is needed for the body's prevailing sodium and volume status.[1] This is autonomous of its usual main chronic regulator, renin/angiotensin II, circulating levels of which are usually suppressed.[1] Over time, the resulting excessive retention of sodium at the distal tubule leads to the development of hypertension. In exchange for the retained sodium, potassium and hydrogen ions are excreted and, if this is prolonged and severe enough, hypokalaemia and metabolic alkalosis may occur.[1]

Why should we screen for primary aldosteronism?

Case detection is of considerable potential benefit to affected individuals. In patients with unilateral primary aldosteronism (usually due to an aldosterone-producing adenoma; Figure), unilateral adrenalectomy results in cure or improvement in hypertension and correction of hypokalaemia (when present) and an improvement in quality of life, which is often marked.[2-4] In patients who do not have surgery, including those with bilateral primary aldosteronism (bilateral adrenal hyperplasia), medical treatment with agents that antagonise aldosterone action can have profound beneficial effects on hypertension and hypokalaemia.[5,6]

Contrary to traditional thinking, primary aldosteronism is not uncommon, and is probably the most common cause of specifically treatable and sometimes curable hypertension. Most recent studies have reported prevalence rates of between 5 and 15% of people with hypertension and most patients are normokalaemic.[7,8] In patients with resistant hypertension, the prevalence rates of primary aldosteronism have consistently been significantly higher, at least 20%.[9,10]

It has become apparent that an excess of aldosterone in patients with primary aldosteronism induces injury (i.e. inflammation, remodelling and fibrosis) in cardiovascular and renal tissues and induces adverse metabolic effects in ways that are at least partly independent

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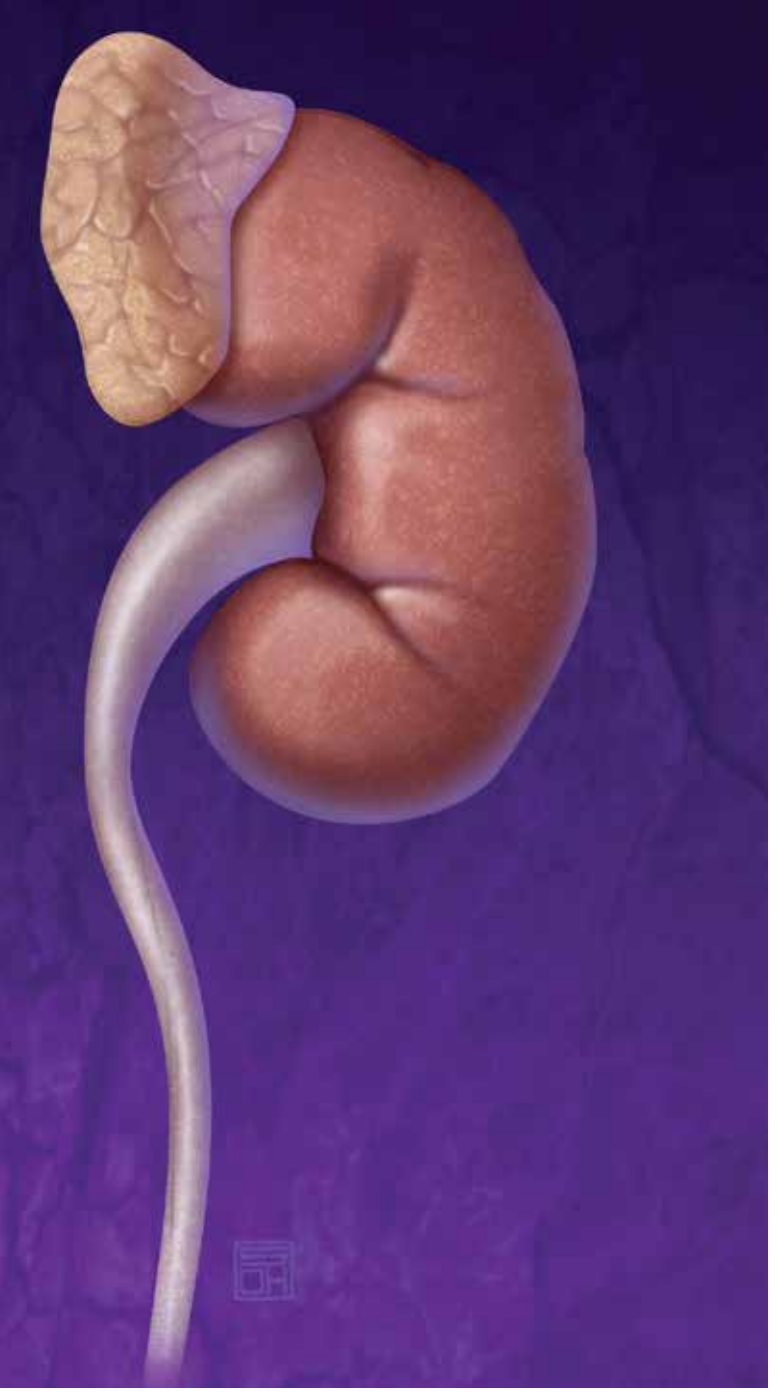

of its effect on blood pressure. As a result, rates of cardiovascular events, including arrhythmias, myocardial infarctions, strokes and mortality, are higher in patients with primary aldosteronism than among those with essential hypertension matched for blood pressure level.[11-13] Just as primary aldosteronism causes more than just hypertension, so does specific treatment against excessive aldosterone action provide more benefit than just lowering blood pressure. Most importantly, the increase in cardiovascular morbidity is reversed following treatment.[11] These data provide compelling support for early detection of individuals with primary aldosteronism who can then benefit from improved cardiovascular outcomes afforded by specific surgical and medical treatments.

In addition to the target organ effects discussed above, evidence is mounting that primary aldosteronism brings about adverse psychological effects and is associated with reduced quality of life. Symptoms of lethargy, fatigue, difficulty concentrating and increased proneness to demonstrations of anger are frequent and usually resolve rapidly following adrenalectomy for unilateral primary aldosteronism.[14] Although less dramatic and rapid, beneficial effects are also seen with specific medical treatment.[15] One contributing factor may be obstructive sleep apnoea, which is common in patients with primary aldosteronism and is possibly a pathophysiological consequence of it.[16] The above findings again argue for early diagnosis and institution of specific treatment of primary aldosteronism.

Key points

- **Primary aldosteronism is more common than is realised.**
- **All patients presenting with hypertension and those with difficult to control or treatment-resistant hypertension should be screened for primary aldosteronism.**
- **Primary aldosteronism has more profound cardiovascular consequences per millimetre of blood pressure than other forms of hypertension.**
- **Primary aldosteronism is specifically treatable and potentially curable.**
- **The presence of hypokalaemia is not essential for the diagnosis of primary aldosteronism.**

Who to screen

Screening for primary aldosteronism should be considered in all patients with hypertension, not just those with hypokalaemia or resistant hypertension, because patients with primary aldosteronism may be normokalaemic and have all grades of hypertension according to the stage of development of the disease. A good time to screen is at the time of diagnosis of hypertension, before antihypertensive medications are commenced. This is because medications can affect the results, and the blood pressure response to specific surgical or medical treatment for primary aldosteronism reduces with increasing duration of hypertension.

How to screen

The plasma aldosterone/renin ratio (ARR; see the box) is currently the best available screening test for primary aldosteronism.[17] Screening sensitivity is improved by collecting blood midmorning from patients while seated after being upright for two to four hours. Fasting is not required. As hypokalaemia can result in a lowering of plasma aldosterone levels, this should be corrected if possible by slow-release potassium chloride supplements before excluding primary aldosteronism on the basis of a normal ARR. Patients should be encouraged not to restrict their dietary sodium intake before testing because dietary sodium restriction can 'unsuppress' renin levels and therefore lead to false-negative ARR results.

Medications causing false-negative and false-positive ARR screening results

Medications that stimulate renin and can cause false negatives include diuretics (such as spironolactone), dihydropyridine calcium channel

A suggested approach for measurement of the ARR

Before ARR measurement

- Correct hypokalaemia, if present, with slow-release potassium chloride supplements
- Avoid factitious rises in plasma potassium by ensuring blood is collected slowly using a syringe and needle (avoid Vacutainers™), avoiding fist clenching during collection, waiting 10 seconds or longer after tourniquet release and ensuring separation of plasma from cells within 30 minutes
- Encourage patient not to restrict sodium intake
- Where possible, withdraw medications that significantly affect the ARR:
  - at least two weeks before blood collection for beta blockers, clonidine, methyldopa, NSAIDs, ACE inhibitors, ARBs, dihydropyridine calcium channel blockers
  - at least four weeks before blood collection for diuretics – both potassium sparing (e.g. spironolactone, eplerenone, amiloride and triamterene) and potassium wasting (e.g. hydrochlorothiazide, chlorthalidone, indapamide and frusemide)
- Where necessary to maintain hypertension control, commence other antihypertensives that have lesser effects on the ARR (verapamil slow-release ± hydralazine and/or prazosin)
- Oestrogen-containing oral contraceptive agents may lower renin concentration and cause false-positive ARR results when plasma renin concentration is measured rather than plasma renin activity. Do not withdraw unless confident of alternative, effective contraception

Conditions for collection of blood

- Mid-morning, after patient ambulant for at least two hours, seated for five to 15 minutes
- Careful collection technique avoiding stasis and haemolysis

Factors to take into account when interpreting results

- Age – in patients over 65 years, renin can be lowered more than aldosterone by age alone, leading to a raised ARR
- Sex – ARR is higher in females and is affected by the phase of the menstrual cycle; risk of false positives during luteal phase, but only if calculated using plasma renin concentrations rather than plasma renin activity
- Time of day, recent diet, posture and length of time in that posture
- All medications
- Method of blood collection and any difficulty (could lead to factitious rises in potassium)
- Level of potassium
- Level of creatinine (renal failure can lead to false-positive ARR)
- Assay methodology – could there be a problem?

ABBREVIATIONS: ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; ARR = aldosterone/renin ratio.

blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers.[17] It was recently reported that selective serotonin reuptake inhibitors (SSRIs) also lower the ARR.[18]

Beta blockers, methyldopa, clonidine and NSAIDs suppress renin, raising the ARR with the potential for false positives.[17] Whether moxonidine can affect the ARR remains uncertain, but as

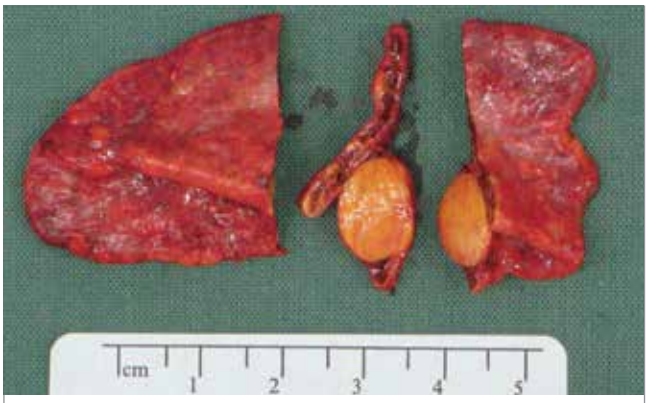

Figure. Right adrenal gland containing an aldosterone-producing adenoma (centre) removed from a 46-year-old woman. Surgery led to cure of hypertension and marked improvement in quality of life.

moxonidine treatment leads to reduced sympathetic nerve activity (as does clonidine), it may be expected to reduce renin levels leading to false-positive ARR values.

Getting around the confounding effects of medications

When feasible, diuretics should be ceased at least four weeks before ARR measurement and other interfering medications ceased at least two weeks before. During this time, hypertension control should be maintained, if necessary, using other agents that do not interfere with the ARR, such as slow-release verapamil (usually 240 mg tablets given as half a tablet twice daily) to which can be added hydralazine (starting at 12.5 mg twice daily) and/or prazosin (starting at 0.5 mg twice daily). It is important not to use hydralazine without protecting against reflex tachycardia by concomitantly giving slow-release verapamil.

In cases where a potentially interfering medication cannot be withdrawn, useful information can still be obtained by taking into account its known effects when interpreting the ARR result. For example, a raised ratio in patients receiving a diuretic, ACE inhibitor, angiotensin receptor blocker, dihydropyridine calcium blocker or SSRI antidepressant would make the diagnosis of primary aldosteronism very likely, whereas a normal ARR in the presence of beta blocker treatment would make the diagnosis very unlikely.

Other causes of false-negative and false-positive ARR results

False negatives occur during pregnancy and in patients who also have renovascular forms of hypertension.

False positives may occur in patients with renal dysfunction or advancing age. False positives are more common among women and can occur while taking oestrogen-containing oral contraceptives but only if the ARR is calculated using direct renin concentration rather than plasma renin activity.[19,20]

When to refer

The ARR is a screening test only and should be repeated once or more before deciding whether to proceed to further workup. If it remains

persistently elevated, and the patient wishes further assessment, then referral to a physician with expertise in the management of patients with endocrine hypertension is recommended as the subsequent steps of diagnostic workup are complex and may require inpatient admission. If possible, commencement of spironolactone and amiloride (agents that antagonise aldosterone action) should be avoided until the workup is completed because these agents will confound test results and require a long wash-out period after cessation.

Confirming the diagnosis

A repeatedly positive ARR should lead, if the patient wishes it, to confirmatory testing.[21] This usually involves measuring plasma aldosterone during the administration of either oral fludrocortisone acetate and slow-release sodium chloride (fludrocortisone suppression testing) or intravenous saline (saline suppression testing). Failure of aldosterone to suppress during these manoeuvres definitively confirms primary aldosteronism.

A positive confirmatory test should lead, if the patient wishes it, to adrenal venous sampling and adrenal CT scanning.[21]

Treatment

Lateralisation on adrenal venous sampling (one normal adrenal suppressed in terms of aldosterone production) leads to the option of a surgical approach and possible cure (about 50% overall, almost 80% in young female patients) or a significant improvement (the remainder) in blood pressure control.

If lateralisation is not seen on adrenal venous sampling, or the patient declines surgery, specific drugs inhibiting aldosterone action such as amiloride and spironolactone can be employed in the lowest dose necessary to achieve control of hypertension. When side effects of spironolactone are seen (for example, gynaecomastia, loss of libido and menstrual irregularities due to its effects on sex steroid receptors), the dose should be lowered and amiloride added. Eplerenone is also effective for treatment of primary aldosteronism and more specific as a mineralocorticoid receptor antagonist than spironolactone, so is less likely to cause sex steroid-related side effects. However, it is currently not available as a subsidised item through the PBS for the treatment of patients with hypertension (including primary aldosteronism) in Australia.

Only small doses (for example, 12.5 to 50 mg daily of spironolactone and/or 2.5 to 20 mg daily of amiloride) are usually required for an optimal antihypertensive effect. Patience is needed as the full effect of each dose level takes weeks or months to be achieved. These medications correct hypokalaemia quickly in all but the most severe cases of primary aldosteronism, and potassium supplements should therefore usually be ceased when spironolactone and amiloride are commenced. Overtreatment with these agents can cause volume contraction with prerenal failure, rising creatinine concentrations and potentially life-threatening hyperkalaemia. They should therefore be used with great caution in patients with existing renal impairment, and electrolytes and renal function should be regularly checked.

Conclusion

Primary aldosteronism is common and is associated with morbidity that is excessive for the degree of hypertension but which can be effectively prevented or reversed by specific treatment. ARR testing should therefore be considered for all patients with hypertension. Knowledge of confounding factors and how to avoid them will aid in achieving optimal detection. **ET**

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

COMPETING INTERESTS: None.

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