Investigation of endocrine causes of secondary hypertension

PATRICIA WHITFIELD MBChB
RICHARD W. CARROLL MBChB, FRACP
JEREMY KREBS MBChB, MD, FRACP

This section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

Hypertension affects 31.6% of the adult population in Australia and despite recent medical advances, 50% of hypertensive patients have suboptimal blood pressure control.[1-2] An estimated 9.4 million deaths per year can be attributed to hypertension,[3] largely due to cardiovascular disease, stroke and kidney failure.

At least 10% of patients have a secondary cause for hypertension (see Box 1), which, if not recognised, may lead to resistant hypertension.[2] This is defined as blood pressure above recommended targets despite use of three antihypertensive medications, including a diuretic, or controlled blood pressure with use of four agents.[4] The identification of secondary causes is important due to increased morbidity and mortality associated with these conditions.

Appropriately selecting patients to investigate for secondary causes of hypertension is difficult because of the high prevalence and costs involved. Guidelines suggest investigating patients with refractory hypertension or an 'absence of usual factors' that are suggestive of essential hypertension, such as family history, gradual onset, high salt intake and obesity. Screening is also recommended in the setting of unusual clinical or laboratory findings, such as hypokalaemia, tachycardia or renal impairment, as well as in patients with sudden onset, intermittent or labile hypertension.[5]

The following cases illustrate an approach to the investigation of more commonly considered endocrine causes of hypertension.

Case 1. A 63-year-old obese man has a longstanding history of hypertension and is treated with 10 mg perindopril, 47.5 mg metoprolol controlled release and 10 mg felodipine. He has hypercholesterolaemia and a strong family history of hypertension. A recent blood pressure recording is 160/82 mmHg, and investigations reveal a potassium level of 3.0 mmol/L, consistent with previous recordings.

Although the patient has risk factors for essential hypertension, the presence of hypokalaemia and poorly controlled hypertension suggests that further investigation is warranted.

What initial investigations should be performed?

A full history and examination targeted to secondary causes of hypertension is required. In this case, the presence of hypokalaemia raises the possibility of primary aldosteronism (PA). The most appropriate screening test is the concurrent measurement of serum aldosterone and renin concentrations so a ratio of the two values (aldosterone to renin ratio [ARR]) can be calculated.[6] Results show:

- aldosterone 330 pmol/L (normal range: 100–800 pmol/L)
- plasma renin activity 0.3 pmol/mL/hr (normal range: 0.4–2.3 pmol/mL/hr)
- ARR 1100.

What is the likely diagnosis in this man?

An ARR of more than 750 is suggestive of PA. This is a common condition (affecting 2 to 10% of people with hypertension) and may be secondary to an adrenal adenoma, bilateral

1. Secondary causes of hypertension

Renal
Chronic kidney disease
Renovascular disease (arteriosclerotic disease, fibromuscular dysplasia)

Endocrine
Primary aldosteronism
Cushing's syndrome; other forms of glucocorticoid excess
Phaeochromocytoma/paraganglioma
Hypo/hyperthyroidism
Parathyroid disease
Acromegaly

Medications/drugs
High-dose oestrogens
Antidepressants (monoamine oxidase inhibitors, tricyclic antidepressants)
NSAIDs
Erythropoeitin
Cyclosporin/tacrolimus
Appetite suppressants
Cocaine
Carbamazepine
Decongestants
St John's wort
Liquorice

Other
White-coat hypertension
Obstructive sleep apnoea
Coarctation of the aorta
Acute spinal cord section
Acute increased intracranial pressure
Gestational hypertension/pre-eclampsia

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Dr Whitfield is an Endocrinology Advanced Trainee at the Endocrine, Diabetes and Research Centre, Wellington Regional Hospital, Wellington. Dr Carroll is an Endocrinologist at the Endocrine, Diabetes and Research Centre, Wellington Regional Hospital and at the Department of Medicine, University of Otago (Wellington Campus), Wellington. Dr Krebs is an Endocrinologist and Clinical Leader at the Endocrine, Diabetes and Research Centre, Wellington Regional Hospital, Wellington and Clinical Senior Lecturer at the Department of Medicine, University of Otago (Wellington Campus), Wellington, New Zealand.

SERIES EDITOR: Dr Bernard Champion BEc, MB BS, BSc(Med)(Hon 1), FRACP, MMedEd is a Lecturer at Sydney Medical School Nepean and The University of Sydney; and Head of Department at Endocrinology and Diabetes, Nepean Blue Mountains Local Health District, Penrith, NSW.

adrenal hyperplasia or rarer causes, such as a familial condition. GPs should have a low threshold for screening for PA, particularly in patients under 50 years of age. Contrary to popular belief, hypokalaemia is not present in the majority of patients, and screening should not be restricted to this population.[6]

How confident are we in this diagnosis?

ARR has a sensitivity of 64 to 100% for the detection of PA.[7] To improve accuracy, renin and aldosterone should be tested in the morning. Hypokalaemia should be corrected first as it reduces aldosterone secretion, falsely lowering the ARR. Although most antihypertensives affect ARR to varying degrees, it is generally considered acceptable to perform initial screening tests while the patient is taking their usual medications, with the exception of mineralocorticoid antagonists (spironolactone, eplerenone), which must be stopped at least four to six weeks before testing.[6-7] If PA is highly suspected but not confirmed on screening, repeat testing after antihypertensive withdrawal is appropriate. Slow-release verapamil and alpha-blockers (doxazosin, prazosin) affect ARR minimally and may be used as alternative antihypertensive agents before repeat testing.

What investigations should be performed next?

At this stage, referral of the patient to an endocrinologist should occur for confirmatory testing. The most frequently used test is the normal saline suppression test. In this patient, the aldosterone level remained at 358 pmol/L (<140 pmol/L excludes the diagnosis), confirming PA. An abdominal CT scan demonstrated a right-sided adrenal lesion, and adrenal venous sampling confirmed lateralisation of aldosterone secretion to this side.

How should this man be treated?

Patients with PA have increased rates of cardiovascular disease and stroke compared with those with essential hypertension, and thus definitive treatment is important.[8] Surgery is the most appropriate treatment for patients with an adrenal adenoma, with resolution of hypokalaemia and improvement in hypertension in nearly 100% and 'cure' of hypertension in 50%.[6] For patients with bilateral adrenal disease or contraindications to surgery, long-term mineralocorticoid antagonist treatment, using spironolactone, eplerenone or amiloride, is required.

Case 2. A 54-year-old man with type 2 diabetes has a blood pressure reading of 130/84 mmHg while taking 20 mg accupril twice daily, 190 mg metoprolol controlled release, 2.5 mg bendrofluazide and 10 mg felodipine. In the past year, his glycaemic control has deteriorated significantly despite introducing insulin. He describes increasing weight and low mood. On examination, he has evidence of proximal muscle weakness, central obesity and easy bruising. Blood tests show an elevated HbA_{1c} of 9.5% (80 mmol/mol).

What initial investigations should be performed?

Investigation for hypercortisolaemia is required. Appropriate initial screening tests include a 24-hour urinary free cortisol (UFC), an overnight dexamethasone suppression test (DST) or midnight salivary cortisol (as midnight serum cortisol is impractical). The measurement of serum cortisol alone is not an appropriate screening method for hypercortisolaemia.

In this case, 24-hour UFC levels are measured, demonstrating an excretion of 935 nmol/day (normal range: 50–250 nmol/day).

What is the likely diagnosis?

Elevated UFC is suggestive of hypercortisolaemia (Cushing's syndrome [CS]). CS is rare, affecting 0.5 to 1% of patients with hypertension. The diagnosis is challenging not least because numerous conditions may be associated with apparent hypercortisolaemia on testing in the absence of true disease (see Box 2).[9]

How confident are we in this diagnosis?

The sensitivity of each of the screening tests is high; however, because of poor specificity, at least two screening tests should be performed. If negative, a diagnosis of CS can usually be excluded, but clinicians may elect to reassess the patient at six months and retest if there are new clinical signs.[9] Although overt CS is readily diagnosed, more subtle symptoms (uncontrolled hypertension or diabetes, unexplained osteoporosis or psychiatric disturbances) may warrant exclusion of this diagnosis. The most discriminating features of CS include the presence of catabolic features, such as purple abdominal striae, proximal myopathy and easy bruising.

2. Conditions that may be associated with hypercortisolaemia[9]

Overlap of clinical features with Cushing's syndrome

Pregnancy
Depression and other psychiatric conditions
Chronic alcohol use
Glucocorticoid resistance
Morbid obesity
Poorly controlled diabetes

No clinical features of Cushing's syndrome

Physical stress
Malnutrition
Anorexia nervosa
Intense chronic exercise
Hypothalamic amenorrhoea
Cortisol binding globulin excess

The DST is falsely elevated in 50% of women taking the combined oral contraceptive pill due to the effects of exogenous oestrogen on cortisol-binding globulin. Midnight salivary cortisol test is not appropriate in shift workers and UFC levels may be reduced in people with renal impairment. Because of its poor specificity, falsely elevated UFC levels are common when readings are less than four times the upper limit of normal.[9] To improve specificity, UFC and midnight cortisol tests should be performed twice.

In this patient, a DST is performed for confirmation. Serum cortisol fails to suppress to less than 50 nmol/L, which is strongly suggestive of hypercortisolaemia.

What investigations should be performed next?

Once CS is suspected on the basis of clinical features and one or more screening test, the patient should be referred to an endocrinologist. Once CS is confirmed, an assessment for adrenocorticotropic hormone (ACTH) dependence or independence is required. ACTH-dependent CS is most commonly the result of a pituitary tumour (Cushing's disease) but is occasionally due to ectopic ACTH production. ACTH-independent CS is due to primary adrenal excess cortisol production.

In this patient, ACTH levels were elevated

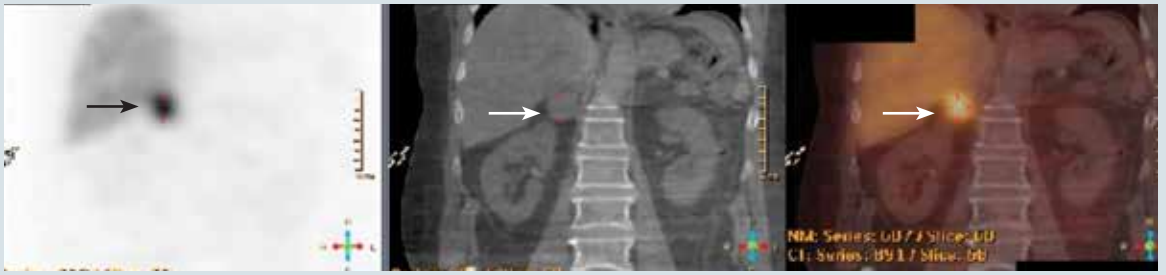

Figure. 123-MIBG and CT images demonstrating right adrenal phaeochromocytoma (arrows) in Case 3.

at 23 pmol/L (normal range: 1.8–11.9 pmol/L) suggesting ACTH dependence, and a pituitary MRI demonstrated a pituitary adenoma. Petrosal sinus sampling of ACTH may be performed to confirm a pituitary source if the MRI scan is negative.

How should this man be treated?

Without treatment, five-year survival is less than 50%.[10] Surgical resection allows best chance of cure, with improvement in hypertension in 75%.[5] Perioperative treatment with oral inhibitors of steroidogenesis may be required. In pituitary disease, surgical remission occurs in 60%, with others requiring medication or radiotherapy.

The patient successfully underwent pituitary surgery and an ACTH-secreting adenoma was confirmed histologically. He is now normotensive on only one agent and has significantly improved glycaemic control (current HbA_{1c}, 6.7% or 50 mmol/mol).

Case 3. A 73-year-old man undergoes a CT scan of his abdomen because of rectal bleeding. The CT scan shows a 2 cm incidental adrenal lesion. He has a history of hypertension while taking perindopril 10 mg, metoprolol controlled release 95 mg and doxazosin 4 mg. He describes symptoms of postural hypotension but is otherwise well. Examination and routine blood tests are unremarkable aside from a mild postural drop.

What initial investigations should be performed?

In the context of an adrenal incidentaloma, a full screen for adrenal hypersecretion (hypercortisolaemia, catecholamine excess and hyperaldosteronism) is required.

On screening, results show:

- plasma normetadrenaline 1860 pmol/L (normal, <900 pmol/L)
- plasma metadrenaline 756 pmol/L (normal, <500 pmol/L).

What is the likely diagnosis in this man?

The elevated metadrenaline levels suggest pathological catecholamine excess, making phaeochromocytoma a possible diagnosis. Although many typical symptoms of phaeochromocytoma (headache, palpitations, anxiety, flushing) are not present, orthostatic hypotension is a recognised feature.[11]

How confident are we in the diagnosis?

Phaeochromocytoma is rare, affecting 0.1 to 0.6% of patients with hypertension.[12] A missed diagnosis can be life-threatening and a test with high sensitivity is therefore important. Plasma metadrenaline, which are metabolites of adrenaline and noradrenaline, confer the highest sensitivity (99%). However, the test is less specific (89%), and false positives are common, especially if results are less than two to three times the upper limit of normal.[11] Direct measurement of adrenaline or noradrenaline is best performed via a 24-hour collection of urine but the sensitivity is reduced (86%). False-positive catecholamine or metadrenaline results can occur with concurrent use of antidepressants, monoamine oxidase inhibitors, amphetamines, labetalol or levodopa and, in this situation, testing should be discussed with an endocrinologist. Any situation of increased physiological stress, such as recent surgery or obstructive sleep apnoea, may also falsely elevate results, and testing should not be performed in the acutely unwell patient.[13]

What investigations should be performed next?

Positive tests should prompt referral of the patient to an endocrinologist. A CT abdomen should be performed to assess tumour location. Nuclear scintigraphy may be required to confirm areas of catecholamine excess, including the possible presence of metastases.

In this patient, plasma metanephrine levels were more than two times the upper limit of normal and a 123-MIBG scan demonstrated avid uptake in the right adrenal gland, corresponding to the previously noted lesion, consistent with a phaeochromocytoma (Figure).

How should this man be treated?

Definitive treatment for phaeochromocytoma is surgical. Patients require careful perioperative blood pressure management and alpha-blockade, usually with phenoxybenzamine or doxazosin. Beta-blockade and volume expansion with normal saline may also be required perioperatively.[11] Improvement in hypertension postoperatively is seen in 75% of patients, with 50% of patients weaned off all medications.[5,11] Of phaeochromocytoma, 30% are associated with inherited germline mutations. The endocrine team can determine whether other screening is required.[14]

This patient proceeded to laparascopic adrenalectomy with significant improvement in blood pressure control postoperatively.

Are there any other considerations?

Histology is usually unable to differentiate between benign and malignant phaeochromocytoma, and postoperative recurrence rates are almost 20%.[11] GPs should monitor regularly for deteriorating blood pressure or new symptoms as this could represent disease recurrence.

Summary

Endocrine disorders may account for up to 10% of cases of hypertension. Once a secondary cause of hypertension is considered, all patients should undergo an assessment for PA. The measurement of plasma metadrenaline should be considered, especially in the context of a strong family history of hypertension, whereas investigations for CS should only occur in the presence of suggestive clinical features. **ET**

References

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

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