Endocrine hypertension

Mark Sherlock

Isolda Frizelle

Abstract

Up to 10% of patients have a secondary cause for hypertension. Endocrine conditions associated with hypertension include diseases associated with mineralocorticoid excess, phaeochromocytomas/paragangliomas, acromegaly and primary hyperparathyroidism. Primary hyperaldosteronism (PH) is the most common endocrine cause of hypertension. If not appropriately managed, PH has an unfavourable cardiovascular morbidity and mortality profile. It is treatable by medical or surgical approaches. Phaeochromocytomas and paragangliomas are rare neuro-endocrine tumours frequently associated with genetic abnormalities.

Keywords Adrenal adenoma; Cushing's syndrome; endocrine hypertension MRCP; paraganglioma; phaeochromocytoma; primary hyperaldosteronism

Key points

- Endocrine causes of secondary hypertension are common
- Endocrine hypertension is the aetiology in up to 10% of patients with hypertension, and more in patients with resistant hypertension
- Screening for secondary causes of hypertension is suggested for high-risk groups
- Appropriate screening for primary hyperaldosteronism can lead to targeted therapy (medical and surgical), which can lead to resolution of hypertension
- Appropriate perioperative management of phaeochromocytomas/paragangliomas (PPGLs) is essential, and these tumours should be managed in specialist centres
- PPGLs are increasingly recognized as having an underlying genetic aetiology
- Diagnosis offers the potential for cure of hypertension and identification of important familial disorders (e.g. PPGL syndrome)

Introduction

Endocrine disorders are estimated to account for up to 10% of all hypertension (Table 1). A low index of suspicion is therefore required to avoid overlooking a potentially curable cause. In recent years, the molecular basis of many causes of endocrine hypertension has been established, in particular the underlying aetiology of primary hyperaldosteronism (PH) and phaeochromocytomas/paragangliomas (PPGLs).

Primary hyperaldosteronism

PH is the most common cause of endocrine hypertension, and is most commonly the result of hyperplasia of, or an adenoma arising from, the zona glomerulosa of the adrenal gland. Increased aldosterone secretion leads to retention of sodium and water in the distal renal tubule, resulting in hypertension with an associated suppression of plasma renin activity. Increased understanding of the molecular mechanisms of PH have revealed somatic mutations in a variety of genes, including *KCNJ5*, *ATP1A1* and *CACNA1D*, which increase intracellular calcium and thus facilitate aldosterone secretion.[1]

Screening for primary hyperaldosteronism

In line with the most recent Endocrine Society guidelines,[2] screening is recommended for high-risk groups (Table 2). This

Mark Sherlock *MB BCh BAO MRCPI MD PhD is a Consultant Endocrinologist and Clinical Senior Lecturer at Tallaght Hospital Dublin and Trinity College Dublin, Ireland. He received his postgraduate endocrine training at Beaumont Hospital, Dublin and the Queen Elizabeth Hospital/University of Birmingham, UK. He obtained a postgraduate MD for a thesis studying morbidity and mortality in patients with acromegaly, and a PhD for studies relating to cortisol metabolism in muscle and in patients receiving hydrocortisone therapy. His main clinical and research interests are pituitary and adrenal disease and salt and water homeostasis. Competing interests: none declared.*

Isolda Frizelle *MB BCh BAO MRCPI is a Specialist Registrar in the Department of Endocrinology, Tallaght Hospital Dublin, Ireland. Competing interests: none declared.*

Endocrine conditions associated with hypertension

Mineralocorticoid excess

Low renin, high aldosterone

- Aldosterone-producing adenoma (Conn's syndrome)
- Bilateral adrenal hyperplasia
- Glucocorticoid-remediable (suppressible) (hyper)aldosteronism
- Adrenal carcinoma — rare

Low renin, low aldosterone

- Congenital adrenal hyperplasia
- 11β−Hydroxylase deficiency
- Liddle's syndrome
- Apparent mineralocorticoid excess

Mineralocorticoid/glucocorticoid excess

- Cushing's syndrome
- Corticosteroid therapy

Other

- Phaeochromocytomas/paragangliomas
- Acromegaly
- Primary hyperparathyroidism

Table 1

Please cite this article in press as: Sherlock M, Frizelle I, Endocrine hypertension, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.05.015

Case detection for PH: who should be screened?[2]

- Sustained blood pressure (BP) >150/100 mmHg, at three measurements obtained on different days, Hypertension (BP >140/90 mmHg) resistant to three conventional antihypertensive drugs, or BP controlled when taking four or more antihypertensive medications
- Hypertension and spontaneous (or diuretic-induced) hypokalaemia
- Hypertension and adrenal incidentaloma
- Hypertension and sleep apnoea
- Hypertension and family history of early-onset hypertension or cerebrovascular accident at <40 years of age
- Hypertensive first-degree relatives of patients with PH

Table 2

comprises determination of plasma aldosterone:renin ratio (ARR), and, if the result is positive, one of the confirmatory tests to definitively confirm the diagnosis of PH before imaging. Importantly, patients must be potassium-replete before testing as hypokalaemia suppresses aldosterone production and can give a false-negative result. Several medications lead to alterations in ARR, and this should be taken into account when interpreting the results (Table 3). A positive screening test for PH is a high plasma ARR with plasma aldosterone >15 ng/dl (420 pmol/litre). In the setting of spontaneous hypokalaemia and hypertension, undetectable renin and plasma aldosterone concentration >20 ng/dl (550 pmol/litre), it is suggested that confirmatory testing is not required.[2]

Interfering medications that can lead to false-positive or false-negative ARR results while screening for PH[2]

Agent	Effect on testing
Mineralocorticoid antagonism (e.g. spironolactone, eplerenone, amiloride)	Increased plasma renin activity, variable effect on plasma aldosterone
β-Adrenoceptor blockers, non-steroidal anti-inflammatory drugs	Reduce/suppress plasma renin activity more than aldosterone
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel antagonists	Reduce plasma aldosterone, increase plasma renin activity
Direct renin inhibitors	Reduce plasma aldosterone, can increase or decrease plasma renin concentrations
Products derived from liquorice root	Decrease plasma renin concentrations
Oestrogen or hormone replacement therapy preparations	Increase renin substrate

Source: Modified from Funder et al.[2]

Table 3

Confirmatory tests for primary hyperaldosteronism

No single test is universally accepted as the gold standard to confirm PH; possible confirmatory tests include oral sodium loading, intravenous saline suppression and the fludrocortisone suppression test. Whichever test is used, the premise is to demonstrate failure of aldosterone suppression, which confirms PH.

Imaging for primary hyperaldosteronism

Non-contrast computed tomography (CT) of the adrenal glands is indicated once confirmatory testing is complete. Adrenal vein sampling and/or functional positron-emission tomography (PET) may be required to confirm unilateral secretion of aldosterone, but is only required when surgery is planned (Figure 1).

Management of primary hyperaldosteronism (Figure 1)[2]

Options for treatment of PH caused by an aldosterone-secreting adenoma include laparoscopic surgical excision; for patients who are not surgical candidates, a mineralocorticoid receptor antagonist (spironolactone, eplerenone) is indicated. Surgery is not indicated in bilateral adrenal hyperplasia (treatment is with spironolactone or eplerenone).

Glucocorticoid-remediable aldosteronism (GRA)

The genes encoding aldosterone synthase and the adrenocorticotropic hormone (ACTH)-sensitive 11β-hydroxylase enzyme are 95% identical. In GRA, the promoter of the 11β-hydroxylase gene is fused to the coding region of aldosterone synthase. The product of this hybrid gene is an aldosterone synthase enzyme that is ACTH-sensitive. In individuals with GRA, ACTH increases the activity of aldosterone synthase, resulting in hyperaldosteronism. Treatment with glucocorticoids (to suppress ACTH) is highly effective.

Apparent mineralocorticoid excess (AME)

AME is an autosomal recessive condition associated with a defective 11β-hydroxysteroid dehydrogenase type II enzyme. This enzyme inactivates cortisol through conversion to cortisone in the kidney, preventing cortisol binding to the mineralocorticoid receptor (for which cortisol has the same affinity as aldosterone). In AME, cortisol is able to activate the mineralocorticoid receptor, leading to hypertension and hypokalaemia.

Liddle's syndrome (pseudohyperaldosteronism)

Liddle's syndrome is an autosomal dominant condition in which mutation of the renal epithelial sodium channel (ENaC) produces loss of ability to degrade ENaC, leading to increased sodium retention and resultant hypertension.

Phaeochromocytomas/paragangliomas

Phaeochromocytomas and paragangliomas are catecholamine-secreting tumours arising from the adrenal medulla and extra-adrenal ganglia, respectively. Chromaffin cells produce one or more catecholamines, which are degraded to normetanephrines, metanephrines and 3-methoxytyramine.

In recent years, there has been increased understanding of the pathophysiology of PPGLs. A significant proportion of patients harbour an underlying germline mutation, including in the

Please cite this article in press as: Sherlock M, Frizelle I, Endocrine hypertension, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.05.015