Investigation and management of adrenal disease

Saba P Balasubramanian

Barney Harrison

Abstract

Disorders of the adrenal gland are rare and complex, with many potential pitfalls in their management. An understanding of embryology, anatomy, physiology and biochemistry is crucial. Surgical treatment may be required for syndromes of hormonal excess and/or suspicion of malignancy.

Keywords ACTH; Addisonian crisis; adrenal; adrenalectomy; Cushing's syndrome; MEN syndromes; phaeochromocytoma; pituitary

Anatomy and physiology

This has been covered in detail in a preceding article, but is briefly summarized here. The adrenal glands lie within the renal fascia in relation to the upper poles of the kidneys. The right adrenal gland is located partly behind the inferior vena cava and superior to the kidney, the left adrenal is anteromedial to the kidney. The arterial blood supply arises from the abdominal aorta, phrenic and renal vessels; the main adrenal vein empties into the inferior vena cava on the right and, on the left side, the renal vein. Each adrenal gland consists of an outer cortex derived from mesenchyme and an inner medulla derived from neuroectoderm.

The **adrenal cortex** in turn has three layers.

- The zona glomerulosa is the outer layer, represents 15% of the cortex and produces aldosterone.
- The zona fasciculata is the middle layer, represents 70% of the cortex, and produces cortisol, the sex steroids dehydroepiandrosterone (DHEA) and androstenedione.
- The zona reticularis is the innermost layer and produces sex steroids.

Cortisol synthesis and secretion is upregulated by adrenocorticotropic hormone (ACTH) and corticotrophin-releasing factor (CRF) which are released by the pituitary and hypothalamus respectively. This pathway (the hypothalamo–pituitary–adrenal axis) is controlled by negative feedback. Cortisol mediates the stress response, metabolism of carbohydrate, lipid and protein and, via its mineralocorticoid effects, promotes sodium conservation in the kidney. Aldosterone secretion is under the control of the renin–angiotensin system.[1] It increases renal reabsorption of sodium and excretion of potassium and hydrogen.

Adrenal androgen secretion is under the control of ACTH.

The adrenal medulla synthesizes catecholamines: adrenaline, noradrenaline and dopamine. Adrenaline and noradrenaline act on adrenergic (α1, α2 and β) receptors. These receptors are differentially distributed throughout the body in a variety of organs. In general noradrenaline binds with a greater affinity to α1 and β1 receptors, while adrenaline has a greater affinity for β2 receptors. Dopamine acts predominantly on dopaminergic receptors, which are distinct from adrenergic receptors. These hormones are largely metabolized before being excreted in the urine and measurement of levels of the metabolites in urine and plasma provide a reliable evidence of catecholamine excess in phaeochromocytomas.

Imaging

CT and MRI are commonly used in adrenal imaging to:

- localize the disease in patients with a syndrome of hormonal excess
- confirm morphological abnormalities
- identify features of benign disease (for example lipid-rich lesions) or alternatively features of malignancy (such as heterogeneity, irregular margins and local invasion).

They are essential in the staging of adrenal cancers and in the diagnosis of suspected recurrence (Figure 1).

Adrenal scintigraphy is sometimes used to confirm that a morphological abnormality found on cross-sectional imaging is the source of a proven biochemical syndrome (e.g. meta-iodobenzylguanidine (123I-MIBG) in phaeochromocytoma (Figure 2) and to locate extraadrenal and metastatic phaeochromocytoma. Iodo-cholesterol isotopes (e.g. 59NP) may be used in Cushing's syndrome to assess the functional significance of an adrenal nodule. Single-photon emission computed tomography (SPECT) provides tomographic views of an isotope scan.

18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scanning is useful for the investigation of patients with a lipid-poor 'indeterminate' adrenal mass to:

- provide additional evidence of malignancy (if the maximum standardized uptake value (SUV) >1.8)
- identify occult nodal/systemic metastatic disease.

Imaging–guided selective adrenal vein sampling is often used in Conn's syndrome to distinguish unilateral from bilateral hypersecretion of aldosterone.

Primary hyperaldosteronism

Epidemiology: Primary hyperaldosteronism is caused by excess production of aldosterone from the adrenal cortex. It is thought to be a fairly common cause of secondary hypertension and was found to be prevalent in around 11% of all newly diagnosed hypertensive patients in a large prospective study.

The pathology underlying primary hyperaldosteronism are listed in Box 1.

Clinical features are usually non-specific, with hypertension being the reason for referral in most patients. Hypokalaemia may

Saba P Balasubramanian *MS FRCS (Gen Surg) PhD is a Senior Lecturer and Honorary Consultant Endocrine Surgeon at University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK. Conflicts of interest: none declared.*

Barney Harrison *FRCS is a Consultant Endocrine Surgeon at Royal Hallamshire Hospital, Sheffield, UK. Conflicts of interest: none declared.*

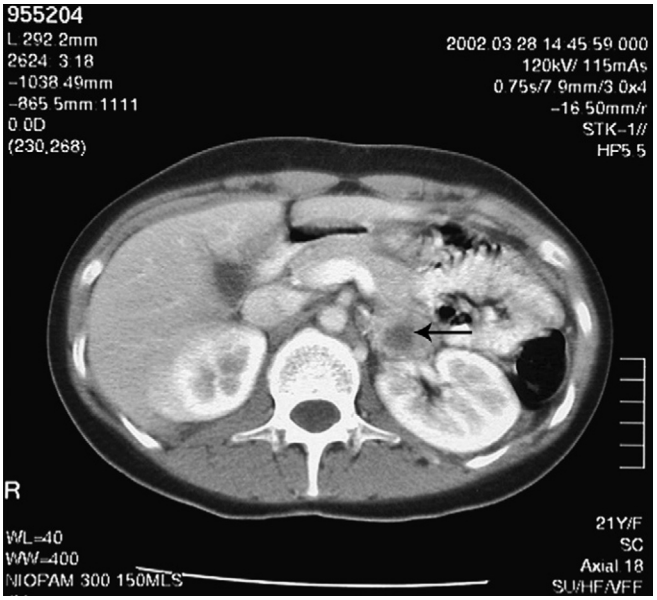

Figure 1

occur in some patients and is associated with fatigue, muscle weakness, and cardiac dysrythmia.

Investigations: The diagnosis of primary hyperaldosteronism should be pursued in:

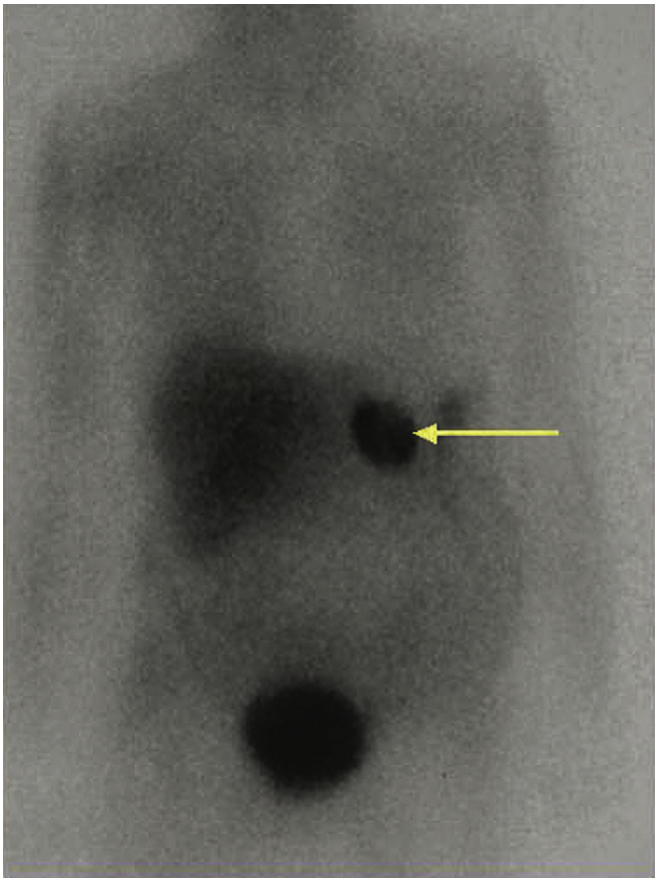

Figure 2

- patients with resistant hypertension
- hypertensive patients with hypokalaemia
- hypertensive patients with adrenal incidentaloma and
- as part of the evaluation in patients where there is a suspicion of secondary hypertension.

A raised aldosterone:renin activity ratio (high aldosterone and low renin levels) in plasma confirms the biochemical diagnosis. CT/MRI is required to assess morphology of the adrenal gland and differentiate unilateral from bilateral gland disease. Selective adrenal vein catheterization to measure the aldosterone—cortisol ratio is used to distinguish unilateral from bilateral disease. This is done routinely in some centres before adrenalectomy and selectively in some centres if the results of cross-sectional imaging are uncertain. Primary hyperaldosteronism must be distinguished from secondary hyperaldosteronism (due to diuretic therapy, renal artery stenosis, malignant hypertension) in which aldosterone and plasma renin concentrations are raised.

Treatment of primary hyperaldosteronism depends on the underlying pathology and primarily involves treating the associated hypertension. This includes medical treatment in all cases and surgery in selected cases with unilateral disease.

Medical treatment includes aldosterone antagonists such as spironolactone and eplerenone in combination with other antihypertensive agents. The side effects of spironolactone include decreased libido and gynaecomastia.

Surgery should be considered for unilateral disease. Cure of hypertension after unilateral adrenalectomy is reported in 30—72% of cases; reduction in antihypertensive medications is likely in the remaining patients. Factors that predict a good response to surgery include a short duration of hypertension, younger age and absence of family history. Surgery is contraindicated in bilateral disease.

Cushing's syndrome

Epidemiology: Cushing's syndrome is caused by prolonged exposure to high circulating concentrations of cortisol. Cushing's syndrome mainly affects adults aged 20—50 years. The annual incidence is 0.7—2.4 per million population.

There are two main types of endogenous Cushing's syndrome: ACTH-dependent (85%) or ACTH-independent (15%). ***ACTH-dependent Cushing's syndrome*** may be caused by:

- pituitary adenoma (Cushing's disease)
- ectopic secretion of adrenocorticotropic hormone (lung cancer, carcinoid, medullary thyroid cancer, thymoma, pancreatic islet cell tumour).

Causes of primary hyperaldosteronism

Common

- Adrenal adenoma (Conn's syndrome)
- Bilateral adrenal hyperplasia.

Rare

- Unilateral adrenal hyperplasia
- Adrenal carcinoma
- Glucocorticoid-suppressible hyperaldosteronism

Box 1