Adrenal disease

INTRODUCTION

ADRENAl disorders have traditionally been considered uncommon and may present insidiously in the primary care setting. However, the increased use of CT imaging has led to an epidemic of adrenal incidentalomas, and recent research has revealed the high prevalence of aldosterone excess as a significant contributor to the burden of hypertension. Furthermore, the increased use of glucocorticoids and immunomodulatory drugs has contributed to iatrogenic forms of adrenal dysfunction.

This How to Treat provides a guide to the diagnosis and management of these relatively common adrenal disorders, as well as the less common but challenging conditions of pheochromocytoma, Cushing syndrome and congenital adrenal hyperplasia.

ADRENAL INCIDENTALOMA

AN adrenal incidentaloma is defined as an adrenal mass lesion greater than 1cm in diameter that is serendipitously discovered by diagnostic imaging in the absence of symptoms or clinical findings suggestive of adrenal disease.[1] It is often 'a disease of ascertainment', a product of the current widespread use of high-resolution imaging.

An incidentaloma is optimally characterised by a dedicated adrenal CT scan; the key question is whether the lesion is benign or malignant (see box 1). It is important to note that more than 7% of the adult population have adrenal tumours – an incidence that increases with age – yet adrenal carcinoma occurs in fewer than two cases per million a year.[2,3] Most of these benign lesions are lipid-rich adenomas, which have a density of less than 10 Hounsfield Units (HU) on a non-contrast CT scan.

CT scan features that further guide the distinction are a smooth, rounded, homogeneous appearance with a diameter of less than 4cm. It is generally recommended that lesions larger than 6cm in diameter are resected, making 4-6cm something of a grey zone, while noting that most lesions larger than 4cm will still be benign.[2]

Although the added value of a CT with contrast is debatable, contrast media washout at 10 or 15 minutes, with absolute washout more than 60% or relative washout more than 40%, is consistent with a benign lesion.[1] MRI can also be used with phase shift to demonstrate lipid content, but it is often more expensive and less accessible. If the non-contrast CT is consistent with a benign adrenal mass (10 HU or less, homogeneous, smaller than 4cm), most guidelines recommend that no further imaging is required.[1,2] Where there is any ambiguity, a further CT scan in 6-12 months is recommended.

Benign adrenal lesions may be functionally active as would be predicted from the biology, with the adrenal cortex synthesising cortisol and aldosterone while the medulla produces catecholamines. This may be clinically reflected in symptoms and signs of Cushing syndrome, primary aldosteronism (PA) or pheochromocytoma respectively; however, in the context of an incidentaloma, the features are, by definition, subtle or occult. Hypertension should lead to further investigation as it may presage a pheochromocytoma, although hypertension may also be associated with Cushing syndrome.

To exclude unrecognised PAGE 31 ▶

Box 1. Causes of adrenal masses

- Cortical adenoma.
- Adrenocortical carcinoma (aldosteron-producing adrenal adenoma [ACC]).
- Pheochromocytoma.
- Congenital adrenal hyperplasia (CAH).
- Massive macronodular adrenal disease.
- Nodular variant of Cushing's disease.
- Neuroblastoma.
- Ganglioneuroma.
- Myelolipoma.
- Haemangioma.
- Cyst.
- Haemorrhage.
- Infiltrative and granulomatous diseases, including TB.
- Lymphoma.
- Metastatic malignancy.

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First published online on 20 May 2022

◀ PAGE 29 or subclinical adrenal disease, the most pragmatic approach is to rule out each of these three possibilities biochemically.

One can argue a lipid-rich lesion (less than 10 HU) is extremely unlikely to be a pheochromocytoma, but most guidelines recommend screening all patients with an adrenal incidentaloma with plasma free metanephrines, which although not specific are very sensitive. Therefore, a normal metanephrine concentration can be taken to exclude a pheochromocytoma.[2] In PA, a serum potassium is useful but not sensitive, so an aldosterone-to-renin ratio (ARR) is the optimal screening test.

Various approaches have been recommended to diagnose subclinical Cushing syndrome (also referred to as mild autonomous cortisol excess), which despite extensive literature, is relatively uncommon. In the absence of overt Cushing syndrome, the authors prefer the overnight dexamethasone suppression test (DST), where 1mg dexamethasone (two 0.5mg tablets) is taken at midnight followed by an 8am cortisol measurement. A 24-hour urinary free cortisol (24h UFC) and/or midnight salivary cortisol estimations may also be used. A serum cortisol concentration of less than 50nmol/L following the overnight dexamethasone suppression rules out Cushing syndrome, with values of less than 70nmol/L likely to be normal. Current guidelines suggest that cortisol levels between 51nmol/L and 138nmol/L should be considered as evidence of 'possible autonomous cortisol secretion' and cortisol levels post-dexamethasone of greater than 138nmol/L should be taken as evidence of 'autonomous cortisol secretion'.[1,2] The overnight DST is a screening test, not a diagnostic test; it is excellent for ruling out Cushing syndrome but does not rule it in. An ambiguous result should, like any screening test, be repeated.

There are a multitude of reasons – that must be further explored – why the cortisol may apparently fail to suppress

For all adrenal masses, where hypersecretion and/or malignancy is suspected, referral to a centre with a multidisciplinary service – including endocrinology, radiology and endocrine surgery – is appropriate to guide management optimally.[2]

ADRENAL HYPERTENSION

Primary aldosteronism

PA is caused by the autonomous secretion of aldosterone by one or both adrenal glands, independent of renin and angiotensin II, and therefore unresponsive to the usual regulatory mechanisms. PA is most commonly caused by an aldosterone-producing adenoma (usually unilateral, also known as Conn syndrome) or bilateral hyperaldosteronism. Much rarer causes include adrenal carcinoma, glucocorticoid-remediable aldosteronism and other familial forms.[4]

Aldosterone acts on the mineralocorticoid receptor (MR) in epithelial and non-epithelial cells. In the kidneys, aldosterone regulates sodium absorption through activation of the epithelial sodium channel, and hyperaldosteronism leads to hypertension and, in some cases, hypokalaemia. Importantly, the MR is also found in non-epithelial cells, including endothelial cells and cardiomyocytes. PA is associated with a higher rate of cardiovascular complications. Compared with patients with essential hypertension (EH) matched for their age, sex and blood pressure, those with PA have higher rates of AF, stroke, coronary heart disease and heart failure.[5] Treatment of PA, especially if instituted early in the disease course, significantly reduces the risk of these complications.[6] Therefore, it is important PA is diagnosed in a timely manner.

PA is the most common endocrine cause of secondary hypertension, affecting 5-10% of people with hypertension in the community and up to 30% in referral centres.[7] However, in a survey of GPs from Victoria, PA was diagnosed in fewer than 0.1% out of more than 7000 hypertensive patients, suggesting significant underdiagnosis.[8] The stereotypical patient with PA develops hypertension with hypokalaemia at a young age; however, hypokalaemia is only present in 30% of patients with PA, and most patients are diagnosed in their 50s.[9] The lack of clinical features that can reliably distinguish PA from EH likely contributes to its underdiagnosis. Since untreated PA is associated with a higher risk of cardiovascular complications, ensure a low threshold when investigating for PA in patients with hypertension.

Screening for PA is based on the ARR.[4] The hallmark of PA is suppres-

sion of renin because of autonomous aldosterone secretion; the ARR will therefore be elevated even if the aldosterone concentration falls within the normal reference range. For most laboratories in Australia, ARR greater than 70pmol/mU (where plasma aldosterone concentration is measured in pmol/L and direct renin concentration is measured in mU/L) is considered a positive test. However, it is important to note that the measurement of ARR can be affected by most of the commonly used antihypertensive medications, salt intake and several other factors (see box 2). Many antihypertensive agents can cause a false-negative ARR, so it is preferable to switch to non-interfering antihypertensive medications for more than two weeks (or more than four weeks for diuretics and more than six weeks for MR antagonists) before checking the ARR (see box 3). It is also important to correct hypokalaemia prior to checking the ARR. ARR should ideally be checked more than once as there can be significant intra-individual variability.[10]

In some patients, switching to non-interfering antihypertensive medications needs to be done cautiously

Because of the difficulty in screening for PA in patients with resistant hypertension who require multiple antihypertensive agents, there is a strong argument for screening at the initial diagnosis of hypertension before initiation of antihypertensive agents.[8 7] In a Victorian study where GPs screened for PA in their treatment-naive hypertensive patients, 35 out of 247 patients screened (14%) were diagnosed with PA.[10A]

Patients with a positive screening ARR are usually referred to an endocrine outpatient clinic where further tests are undertaken (see figure 1). A confirmatory test, the saline suppression test, is generally needed to confirm the non-suppressibility of aldosterone.[4] Following the confirmatory test, lateralisation studies, including CT scanning of the adrenal gland and adrenal vein sampling (AVS), are needed to localise the excess aldosterone production.

AVS is a day procedure performed by highly specialised interventional radiologists; AVS has higher sensitivity and specificity than CT in subtyping

to avoid uncontrolled hypertension.

PA as either unilateral or bilateral.

Unilateral PA can be treated with laparoscopic unilateral adrenalectomy. This often results in resolution of hypokalaemia (if present before surgery) and normalisation of the aldosterone and renin levels. A biochemical cure is more likely if histological analysis demonstrates classical CYP11B2 (aldosterone synthase) staining in the resected aldosterone-producing adenoma (see figure 2).[11] Resolution of hypertension often depends on the duration of hypertension before surgery. Patients with a relatively short duration of hypertension may no longer require antihypertensive treatment, while those with longstanding hypertension may need ongoing antihypertensives because of the vascular damage that accrued over time from untreated PA. However, in the latter cases, blood pressure control usually still improves, and patients need less medication. Bilateral PA requires treatment with an MR antagonist, such as spironolactone. The dose of spironolactone is titrated to achieve normotension, normokalaemia and normalisation of renin (for example, renin concentration of 15-50mU/L). Titration of an MR antagonist to normalise the renin concentration is associated with improved cardiovascular outcomes.[12]

Cushing syndrome

The detection of Cushing syndrome can be challenging as it shares many features with the metabolic syndrome, including obesity, ▸

Box 2. Factors influencing the aldosterone-to-renin ratio (ARR)

- Causes of false-negative ARR:
  - — ACEI.
  - — Angiotensin II receptor blocker.
  - — Diuretics.
  - — Dihydropyridine calcium-channel blockers.
  - — Hypokalaemia.
  - — Dietary salt restriction.
  - — Pregnancy.
  - — Renovascular disease
- Causes of false-positive ARR:
  - — Beta blocker.
  - — Central agonists (clonidine, α-methyldopa).
  - — NSAIDs.
  - — Liquorice.
  - — Renal impairment.
  - — Oral oestrogens.

Box 3. Medications with less impact on the ARR

- Antihypertensive medications with less impact on the ARR:
  - — Verapamil SR 180-240mg daily.
  - — Prazosin 0.5-5mg bd or tds.
  - — Moxonidine 200-400µg daily.
  - — Hydralazine 12.5-50mg bd.

◂ hypertension, diabetes, depression and menstrual irregularity. A recent meta-analysis of 5367 patients reported that the diagnosis was often delayed, on average by 34 months.[13] Findings more specific to Cushing syndrome include proximal myopathy, facial plethora, violaceous abdominal striae (see figure 3), easy bruising, truncal obesity with thin limbs (see figure 3) and intrascapular and supraclavicular fat pads. Also suspect this disease in patients with unusual findings for their age (for example, osteoporosis or hypertension in young adults) or those with adrenal

incidentaloma.

Cushing syndrome is associated with significant morbidity and increased mortality, including a higher risk for venous thromboembolism, stroke, MI and infection.[14] However, unlike PA, endogenous Cushing syndrome is rare; the incidence is 1-2 per million a year.[15]

Screening for Cushing syndrome can be done by measuring the 24h UFC, late night salivary cortisol or by performing the overnight 1mg DST, as discussed earlier. The diagnosis of Cushing syndrome usually requires two out of the three studies to be abnormal.[16] An elevated morning serum cortisol level has limited utility in screening for Cushing syndrome because of the diurnal nature of cortisol secretion, where it is expected to be the highest in the morning.

The most common cause of Cushing syndrome is the use of exogenous glucocorticoids; exclude this before performing further investigations (see Iatrogenic adrenal insufficiency).[16] The second most common cause of Cushing syndrome is pituitary hypersecretion of adrenocorticotrophic hormone (ACTH) from a corticotrope adenoma, also known as Cushing disease.[16] Adrenocortical tumours, which are ACTH independent, account for about 20% of cases of Cushing syndrome.[16] In patients with ACTH-independent disease, where a normal or elevated morning cortisol level is paired with a suppressed ACTH, CT scanning of the adrenal glands is performed seeking an adrenal mass. Resection of a cortisol secreting adrenal adenoma usually results in cure. However, postoperative glucocorticoid therapy is often needed because of pituitary (ACTH) and contralateral adrenal gland suppression, leading to a prolonged period of cortisol deficiency with gradual recovery.

Pheochromocytoma

Pheochromocytoma is a rare catecholamine-secreting tumour arising from chromaffin cells of the adrenal medulla. A similar disease that arises from the sympathetic ganglia is referred to as paraganglioma. The classic triad of symptoms associated with a pheochromocytoma consist of episodic headache, sweating and tachycardia, but this is only found in 25% of cases.[17] Most patients with pheochromocytomas have hypertension that can be exacerbated by the administration of beta blockers.

Measurement of plasma metanephrine and normetanephrine are the preferred screening test, with sensitivity of 97% and specificity of 93%.[18] Twenty-four-hour urine catecholamines also have high sensitivity and specificity for detecting pheochromocytomas if collected accurately. Certain medications, such as antidepressants, and acute illness may lead to a false-positive test. Taper interfering medications and discontinue them for at least two weeks before testing (see box 4).

Localisation studies for pheochromocytoma are performed with CT or MRI of the abdomen and pelvis to detect an adrenal lesion or an extra-adrenal lesion (paraganglioma) that is usually retroperitoneal (see figure 4).[19] If no tumour can be identified on the initial scan, scanning of the of the skull base, neck and thorax, as well as other imaging modalities, may be needed. Patients with pheochromocytoma should be treated initially with alpha-adrenergic blockade (phenoxybenzamine or prazosin). Once adequate alpha blockade has been achieved, a beta blocker can be added to control the tachycardia that often results from alpha blockade. It is important that an alpha PAGE 35 ▶

Box 4. Medications that interfere with plasma and urine metanephrines

- Tricyclic antidepressants.
- Other antidepressants and psychoactive agents (except SSRI).
- Prochlorperazine.
- Levodopa.
- Drugs containing adrenergic receptor agonists, for example, decongestants.

◀ PAGE 32 blocker is started before the beta blocker because blocking the beta-adrenergic receptor — which has vasodilatory actions — without blocking the alpha receptor can result in a hypertensive crisis.

Surgical resection of the tumour is the mainstay of treatment, followed by genetic testing. Most catecholamine-secreting tumours are sporadic. However, it is now recognised, even in pheochromocytomas presenting in an older age group, that a significant proportion have an underlying inherited basis due to germline mutations in the succinate dehydrogenase (SDH) genes or the genes involved in multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome or, less commonly, neurofibromatosis type 1.[19]

ADRENAL INSUFFICIENCY

ADRENAL insufficiency is caused by a failure of cortisol production in the adrenal cortex and may occur secondary to pathology of the adrenal gland (primary adrenal insufficiency, better known as Addison's disease) or hypothalamic or pituitary pathology (secondary adrenal insufficiency). Medication-induced adrenal insufficiency and the concept of 'adrenal fatigue' are also commonly encountered in practice.

Primary adrenal insufficiency

The symptoms of adrenal insufficiency are often non-specific and include fatigue, weight loss, nausea, loss of appetite, depression and anxiety. As a result, the diagnosis can be delayed by years. More specific features are orthostatic hypotension; salt craving; hyperkalaemia, caused by mineralocorticoid (aldosterone) deficiency; and hyperpigmentation of the skin and mucous membranes from increased secretion of ACTH and melanocortin, synthesised with ACTH from pre-pro-opiomelanocortin (see figure 5).

Biochemical features may also include hyponatraemia, anaemia, hypoglycaemia and hypercalcaemia. A prompt diagnosis and adequate hormonal replacement can prevent adrenal crisis, characterised by profound weakness, hypovolaemia and hypotension with impaired consciousness.[20]

Once adrenal insufficiency is suspected, measure a morning serum cortisol and ACTH (see figure 6). Peak cortisol is expected upon waking, so the blood test is ideally done at 8-9am. The diagnosis of primary adrenal insufficiency (or Addison's disease) is highly likely if an early morning cortisol level is less than 140nmol/L in combination with an ACTH concentration elevated more than twofold above the upper limit of the reference range. If the morning cortisol is greater than 365nmol/L, adrenal insufficiency is highly unlikely.[20] For patients who do not require acute glucocorticoid treatment, the corticotropin stimulation test, or short Synacthen test, is the standard confirmatory test. A peak cortisol level below 500nmol/L at 30 or 60 minutes after the injection of 250μg Synacthen indicates adrenal insufficiency.[21] When the cortisol level does not concur with the patient's symptoms, consider factors that increase the cortisol binding globulin, such as pregnancy or oral oestrogen therapy, as they can lead to falsely normal cortisol levels. Midnight salivary cortisol and 24-h UFC measurements are not helpful in the diagnosis of adrenal insufficiency.

The most common cause of primary adrenal insufficiency in adults is autoimmune disease, which typically occurs between the ages of 30 and 50, with a slight female preponderance. Autoantibodies against CYP21A2 (21-hydroxylase) are commonly detected. A spectrum of other autoimmune conditions may also be present; thyroid disease is the most common, as well as vitiligo, type 1 diabetes, primary gonadal failure, coeliac disease and pernicious anaemia.[22]

Screen young males without autoantibodies for adrenoleukodystrophy by measuring very-long-chain fatty acids, as adrenal insufficiency may be the only presenting sign of adrenoleukodystrophy. In CYP21A2 autoantibody-negative individuals, an adrenal CT may be useful to identify infectious or infiltrative diseases, such as TB and tumours.

Treatment of primary adrenal insufficiency includes both glucocorticoid replacement with hydrocortisone (15-25mg a day) or cortisone acetate (20-35mg a day) in two or three divided doses, as well as mineralocorticoid replacement with 9α-fludrocortisone (50-200μg) once daily. Because of an adverse effect on bone and lipid profiles, prednisolone (3-5mg once a day) is only used when compliance is poor. Modified-release glucocorticoids to replicate normal circadian rhythm are undergoing clinical trials. They have been shown to produce significant improvements in body weight and HbA1c compared with standard glucocorticoid replacement, particularly in patients with diabetes mellitus.[23] The titration of glucocorticoid dose is guided by postural blood pressure, body weight, energy levels and symptoms/signs of glucocorticoid insufficiency and excess. The adequacy of fludrocortisone replacement is determined from serum potassium, sodium, renin concentration and blood pressure.[24]

Encourage patients to carry an emergency card/bracelet, and educate them about their glucocorticoid dose and sick-day management in situations of stress, such as gastrointestinal disturbance, infections, surgical procedures and emotional stress. Doubling of their glucocorticoid dose is generally recommended on sick days. Hospital admission for IV hydrocortisone may be necessary if the patient has vomiting, diarrhoea or requires fasting. Unlike glucocorticoid, stress dosing of mineralocorticoid is not required during times of illness or emergencies. Regular education about the absolute requirement for lifelong steroid hormone replacement therapy is crucial for the prevention of adrenal crisis.[25]

Secondary adrenal insufficiency

Hypothalamic or pituitary causes of adrenal insufficiency are different from primary adrenal insufficiency in that adrenal mineralocorticoid production is retained, so electrolyte disturbances are uncommon. Furthermore, the ACTH level is low or suppressed, so abnormal skin pigmentation is not observed.[26] The patient may display other features of hypothalamic–pituitary disease, including visual-field defects. Measurement of anterior pituitary hormones (TSH, free thyroxine, prolactin, LH, FSH, testosterone or oestradiol, growth hormone, insulin-like growth factor) and a pituitary MRI will help to make the diagnosis. Glucocorticoid, but not mineralocorticoid, replacement will be required, together with targeted treatment of the specific aetiology.

Iatrogenic adrenal insufficiency

In patients with a low cortisol and ACTH but no evidence of hypothalamic-pituitary disease, suspect exogenous glucocorticoid exposure. Synthetic glucocorticoids, such as prednisolone and dexamethasone, are – respectively – incompletely or not detected by cortisol assays, which therefore leads to a biochemical picture of adrenal insufficiency. Incongruent clinical symptoms and signs of cortisol excess rather than deficiency may be present (see section on Cushing syndrome).

coids and can occur with any form of administration (oral, inhalation, topical, nasal, intra-articular), dose and treatment duration.[27] Be aware that dexamethasone and betamethasone (long acting) are about 25 times more potent than hydrocortisone (short acting) and more likely to suppress ACTH. Sometimes meticulous history-taking is needed to identify the glucocorticoid; herbal supplements, compounded medicines, skin-whitening creams, intralesional injections (for example, for keloid scars) and intra-articular corticosteroid injections (for example, for arthritis) can all cause adrenal suppression.

Test patients with unexplained symptoms after steroid withdrawal for possible adrenal insufficiency with the short Synacthen test. In those with an insufficient response, initiate treatment with physiological doses of hydrocortisone (20-30mg a day in divided doses) with a plan to wean and review endogenous adrenal function over the ensuing months.

The concurrent administration ▸

True adrenal insufficiency may follow the withdrawal of glucocorti-

◂ of agents that suppress glucocorticoid clearance by the inhibition of CYP3A4 – such as ritonavir, itraconazole, fluconazole, clarithromycin, ciprofloxacin, verapamil and grapefruit juice – can increase the potency of the glucocorticoid and therefore increase the risk of adrenal suppression.

A range of other medications can lead to a low cortisol level; opioids (morphine, fentanyl, tramadol and methadone) may suppress central ACTH production; immune checkpoint inhibitors (such as ipilimumab, pembrolizumab, nivolumab), which are increasingly used for cancer treatment, can cause hypophysitis with isolated ACTH deficiency or even panhypopituitarism; and other agents (such as abiraterone for prostate cancer treatment) can block the steroidogenic pathway.[28] Refer patients with low cortisol from iatrogenic causes to an endocrinologist for further evaluation.

Adrenal fatigue

The term 'adrenal fatigue' is often used in the general media to describe a condition caused by chronic exposure to stressful situations, which leads to adrenal 'overuse' and subsequent failure. However, adrenal fatigue is not a medical condition that is recognised by endocrinology societies. A systematic review of the literature did not identify any consistent relationship between fatigue and the hypothalamic-pituitary-adrenal axis, especially as unsubstantiated methods were used to assess cortisol levels.[29] Careful evaluation of fatigue is required to identify the underlying aetiology – such as adrenal insufficiency, sleep obstructive apnoea, mental illnesses, autoimmune disorders or others – to allow targeted treatment.

ADRENAL INSUFFICIENCY WITH ADRENAL ANDROGEN EXCESS

Genetics and pathophysiology

CONGENITAL adrenal hyperplasia (CAH) is an autosomal recessive disorder characterised by impaired adrenal steroidogenesis. It is most commonly due to mutations in the *CYP21A2* gene, causing a deficiency of the enzyme 21-hydroxylase that is required for both cortisol and aldosterone production.[30] The resulting adrenal insufficiency leads to elevated pituitary adrenocorticotrophic hormone (ACTH), which stimulates the adrenal glands causing hyperplasia and overproduction of cortisol precursors.[31] These precursors, such as 17 hydroxyprogesterone (17OHP), are shunted towards adrenal androgen (DHEA and androstenedione) production.

The clinical phenotype is variable and depends on the residual 21-hydroxylase activity, which is determined by the severity of the mutation in the *CYP21A2* gene.[32] The classic type of CAH affects one in 14,000 to one in 18,000 live births and is a major cause of primary adrenal insufficiency in children and virilised genitalia in the female (46, XX) infants.[33] The non-classic or mild variant is more common, affecting one in 200 to one in 1000 in the population and may present later in life with variable degrees of hyperandrogenism or remain asymptomatic.[34]

Diagnosis and clinical features

Newborn screening for CAH has been in place in many countries and is recommended in Australia; however, the availability is currently state dependent. In infants, 75% of classic CAH presents as the salt-wasting

form and may present with failure to thrive or adrenal crisis (hyponatraemia, hyperkalaemia and shock) within the first three weeks after birth.[35] Prenatal exposure to elevated adrenal androgens in classic CAH causes virilisation and ambiguous genitalia in the female infant, which should prompt biochemical testing for CAH. Central precocious puberty and a reduced final height from premature skeletal maturation and epiphyseal closure may be seen in children with androgen excess from poor control of CAH. Features of hyperandrogenism – such as acne, hirsutism and androgenic alopecia – can be seen in female adolescents and adults. Females with CAH may develop menstrual irregularities, including amenorrhoea and subfertility, while benign testicular adrenal rest tumours (TART) and infertility may be present in males.[31,34]

Non-classic CAH in adolescents and adults may variably present with hyperandrogenism, menstrual irregularities in females and subfertility, which can be very similar to PCOS and thus may only be distinguished by the measurement of 17OHP levels. Individuals with this milder form of CAH have normal cortisol and aldosterone concentrations and may be asymptomatic, especially males.[36]

The diagnostic test is an early-morning 17OHP level (in early follicular phase for menstruating females); a concentration under 6nmol/L excludes the diagnosis and above 30nmol/L is diagnostic of CAH. Synthetic ACTH (Synacthen) stimulation is required for patients with an indeterminate result (6-30nmol/L), and CAH is typically confirmed when the stimulated 17OHP level is more than 30nmol/L.[34] Heterozygotes or carriers may have stimulated 17OHP level that are equivocal or overlapping with normal individuals; therefore, genotyping may be required for detection or for the purpose of genetic counselling.

Treatment and monitoring

Refer all children and adults with CAH to the respective paediatric or adult endocrinologist familiar with the complex management of CAH.[34] Glucocorticoid therapy prevents adrenal crisis from adrenal insufficiency and treats ACTH-mediated hyperandrogenism in classic CAH. However, managing the balance of adequate androgen control and glucocorticoid over-replacement is very challenging, and this conflicting priority may shift through different stages of life. This is firstly due to the inability of currently available glucocorticoid regimens (hydrocortisone, prednisolone, dexamethasone) to mimic the physiological circadian glucocorticoid rhythm. Secondly, exerting negative feedback on ACTH-mediated hyperandrogenism often requires supraphysiological glucocorticoid doses, leading to adverse effects.[31] Mineralocorticoid (fludrocortisone) replacement is also essential in classic CAH to prevent salt wasting and hypovolaemia. Stress dosing with glucocorticoid was covered in the section on adrenal insufficiency.

In children, where the focus of management is to allow timely growth and development, the glucocorticoid of choice is hydrocortisone at 10-18mg/m² a day – ideally, in 3-4 divided doses.[35] To avoid glucocorticoid over-replacement, the aim is not to normalise 17OHP levels but to adjust to a target early-morning 17OHP level between 12nmol/L and 36nmol/L.[31] Long-acting glucocorticoid use is not recommended because of growth suppression and iatrogenic Cushing syndrome. Conversely, poorly controlled hyperandrogenism from glucocorticoid undertreatment leads to accelerated skeletal maturation and precocious puberty. Fludrocortisone replacement typically ranges between 50µg and 200µg daily, adjusted to blood pressure and biochemistry.[31,35] Regular reviews with a paediatric endocrinologist every 3-6 months are recommended.

CAH-related issues in adolescents are challenging and ideally managed in a multidisciplinary setting.[34] In adolescents at puberty, lowest effective doses of hydrocortisone replacement are recommended to avoid growth suppression. In the transition to adulthood, adjustments to the glucocorticoid and mineralocorticoid regimen may be considered. PAGE 38 ▶

◀ PAGE 36 Long-acting glucocorticoid, such as prednisolone, may be useful post-puberty once growth is complete to control issues related to ACTH-mediated hyperandrogenism and to encourage adherence to therapy.[31] Oral contraceptive pills containing drospirenone or cyproterone acetate may be a useful adjunct in females to treat hyperandrogenism and to regulate their menstrual cycles.[31,34] Development of TART in males is seen with inadequate control of CAH; therefore, regular surveillance (every 2-5 years) by testicular ultrasound is recommended.[31] Complex issues – such as sexual function, surgical management of virilised genitalia and fertility in the females – require various specialist assessment. Genetic counsel-

ling is also advised, as an individual with classic CAH has an approximately one in 120 probability of having a child with classic CAH.[34] The management of classic CAH in adults focuses on the long-term balance of glucocorticoid and mineralocorticoid replacement, with the control of hyperandrogenism for fertility, as well as to prevent adrenal crises and adverse effects of glucocorticoid. Hydrocortisone taken 2-3 times daily is recommended for better long-term cardiovascular outcomes and bone health.[31,37,38] There are, however, issues related to adherence to the multiple daily dosing and suboptimum control of hyperandrogenism. Prednisolone can be considered to assist with regulating menstrual cycles and fertility, and its use can be continued during pregnancy if required.[31,39]

In non-classic CAH, glucocorticoid therapy is not recommended for asymptomatic individuals. Therapy is guided by the individual's endocrine requirement because of the highly variable phenotype. The Endocrine Society recommends glucocorticoid for premature puberty and accelerated bone age, subfertility and recurrent miscarriages in adults, or for stress dosing in those with subnormal short Synacthen test.[34] In women with hirsutism, topical management or oral contraceptives, with or without anti-androgen therapy, are preferred over glucocorticoid.[31]

Psychological health

The many complex challenges faced by patients with CAH often create a significant burden on their mental health, reflected by a higher prevalence of psychiatric and substance abuse disorders from observational studies.[40] Common risk factors may be related to adverse effects from therapeutics, growth and pubertal development, body image and self-esteem, and fertility. Gender identity, sexual orientation and stigma stemming from ambiguous genitalia are challenging issues specific to females with classic CAH.[41] Therefore, psychosocial screening and mental health consultations by practitioners familiar with CAH-related issues are recommended.

CASE STUDIES

Case study one

JASON, 37, is referred for evaluation of possible secondary cause of hypertension. He was diagnosed with hypertension at 31 but is otherwise healthy. His medications are telmisartan 80mg daily, amlodipine 10mg daily and potassium chloride 600mg daily. Despite being compliant with both antihypertensives, his blood pressure at home is still greater than 140/90mmHg on most days.

On examination, his BMI is 22kg/m^2, seated blood pressure is 146/95mmHg and his heart rate is a regular 75bpm. He is not Cushingoid in appearance and has a normal cardiorespiratory examination.

Endocrine testing for secondary causes of hypertension reveals normal plasma metanephrines and thyroid function. His ARR is also normal at 14, with corresponding aldosterone of 634pmol/L, renin of 45mU/L and potassium of 3.2mmol/L.

To facilitate further investigations, his antihypertensive medications are changed to verapamil SR 180mg daily, prazosin 0.5mg bd and potassium chloride 2400mg daily. On repeat testing, his potassium is 3.9mmol/L and ARR is 153 (normal less than 70), based on an aldosterone of 1700pmol/L and renin of 11.1mU/L. He undergoes a saline suppression test in the seated position that confirms the diagnosis of PA, or Conn syndrome, with a post-saline aldosterone of 852pmol/L. Adrenal CT does not visualise an adrenal adenoma, but AVS demonstrates right-sided lateralisation of aldosterone excess with contralateral suppression, consistent with a right-sided aldosterone-producing adrenal adenoma.

Jason undergoes a unilateral laparoscopic adrenalectomy after three months of spironolactone treatment (at 75mg a day) to normalise his blood pressure and renin concentration before surgery. Six months after surgery, a biochemical cure of primary aldosteronism is confirmed, with normal ARR of 4, aldosterone of 418pmol/L, renin of 104mU/L and potassium of 3.9mmol/L. His blood pressure is now controlled on amlodipine 5mg daily, and he no longer requires potassium supplementation to maintain a normal serum potassium concentration.

Case study two

Leah, 26, has a history of treated hypothyroidism and presents to her GP with general malaise and fatigue. She has lost 6kg over the past six months, from 70kg to 64kg. She also experienced a three-month history of intermittent vomiting between 5-10 times daily. Her bowel motions are normal. Leah's only medication is thyroxine 75µg daily. She is a non-smoker and does not drink alcohol regularly.

A blood test shows negative tissue transglutaminase antibodies and gastric parietal cell antibodies. Gastroscopy rules out obstructive oesophageal disease. Thyroid hormone replacement is adequate with a TSH of 2.5mL/IU (normal 0.4-4.0). Her sodium level is 132mmol/L (normal 133-146), and she has a low blood pressure, which is felt to be secondary to dehydration. She is encouraged to maintain regular fluid intake and prescribed antiemetics to reduce nausea and vomiting.

Leah returns one month later with ongoing vomiting and weight

loss to 58kg. She is referred to ED.

On examination, she is hypotensive with a blood pressure of 100/55mmHg, decreasing to 85/50mmHg on standing, and tachycardic, with a heart rate of 105bpm. She is noted to have darker skin pigmentation compared with her siblings. Her sodium concentration is low at 129mmol/L, while her potassium concentration is at the upper limit of normal at 5.2mmol/L (normal 3.4-5.3). Her renal and liver function are both normal and random blood glucose is 4.5mmol/L (normal 4-6).

Given her history, examination and biochemical findings, a morning cortisol and ACTH are measured. Her 8am cortisol is 32nmol/L (normal 206-620), with an elevated ACTH of 105pmol/L (normal 4.4-13.3). Subsequent testing reveals a morning aldosterone concentration of 100pmol/L (normal 165-875 but laboratory reference values will vary) with a markedly elevated renin of 168mU/L (normal 8-50pmol/L).

Leah is diagnosed with Addison's disease. She has an elevated 21-hydroxylas antibody titre, consistent with an autoimmune cause.

She is treated with IV hydrocortisone 100mg four times a day and fluids, resulting in improved blood pressure and normalised electrolytes. She is discharged on oral hydrocortisone 20mg mane and 10mg in the afternoon and fludrocortisone 100µg a day. She is educated about the importance of compliance and sick-day management.

CONCLUSION

ADRENAL disorders – endogenous or iatrogenic – can manifest as either an incidental finding or symptoms associated with the excessive production or deficiency of adrenal hormones. The adrenal incidentaloma should be characterised with a dedicated adrenal CT, in addition to the measurement of cortisol, aldosterone and metanephrines.

In patients with hypertension, aldosterone excess is the most common endocrine cause; test for this using the ARR. Pheochromocytoma and Cushing syndrome are much rarer, but exclude these in patients with the relevant symptoms and signs. If clinical features of glucocorticoid excess coexist with a low morning cortisol concentration, exclude exogenous glucocorticoids. Low cortisol, together with an elevated ACTH, is consistent with adrenal insufficiency and requires treatment with both glucocorticoid and mineralocorticoid replacements. Consider CAH when adrenal insufficiency is accompanied by androgen excess.

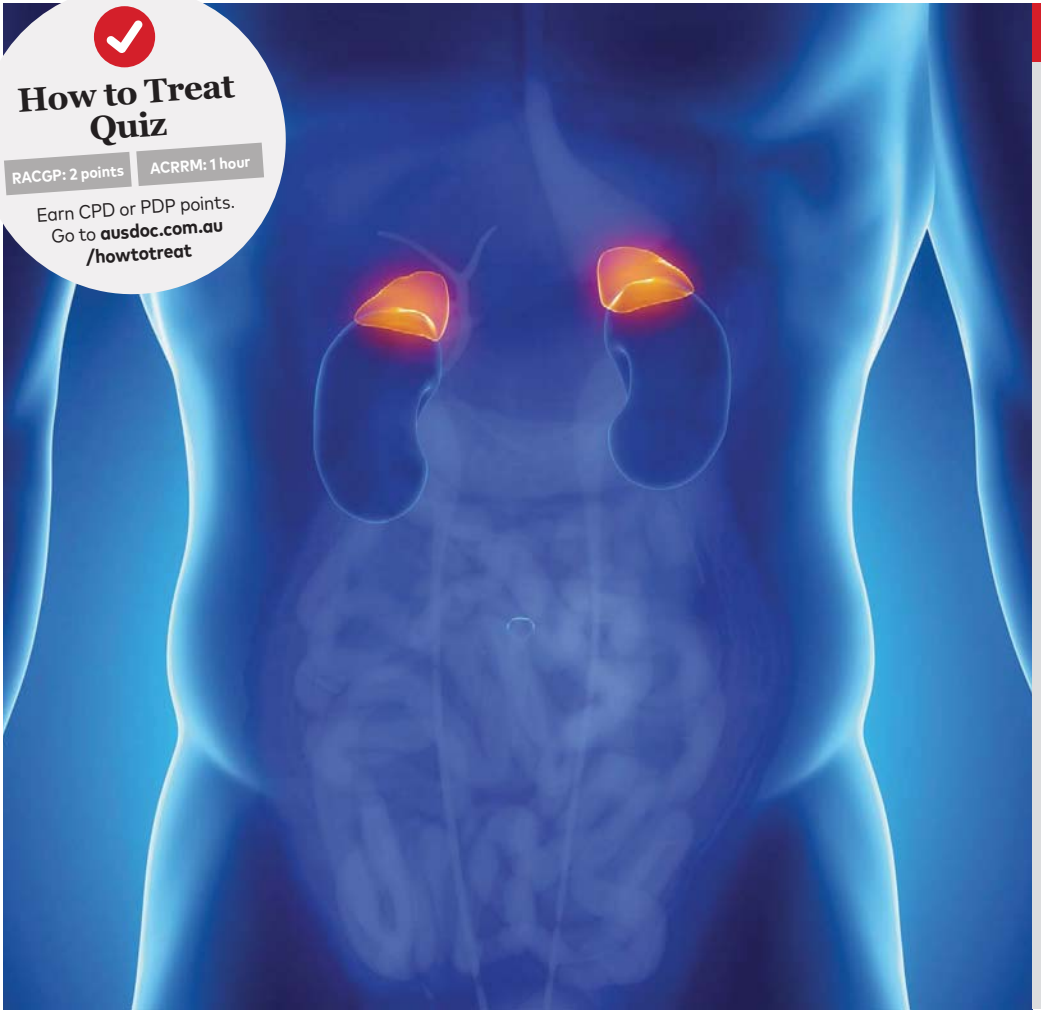
Despite the complexity of adrenal conditions, they can be co-managed in the primary care setting by having an awareness of the related symptoms and signs (or lack of), ordering the most appropriate screening tests and working in collaboration with an endocrinologist.

Acknowledgements

The authors thank Dr Ian Simpson, Dr Elisabeth Ng, Dr Nicholas YN Chee, Dr Jianbin Liu and Professor Ken Lau for their contribution of clinical images and photographs.

References

Available on request from howtotreat@adg.com.au



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NEED TO KNOW

Adrenal incidentaloma can be assessed with a dedicated non-contrast CT scan, an aldosterone-to-renin ratio (ARR), plasma metanephrines and an overnight 1mg dexamethasone suppression test.

Primary aldosteronism (PA) is a common treatable cause of hypertension; this warrants screening in all hypertensive patients, preferably at diagnosis to avoid the confounding effects of commonly used antihypertensives. PA carries higher cardiovascular risk than blood-pressure-matched essential hypertension.

Cushing syndrome may present insidiously mimicking the metabolic syndrome; it can be diagnosed using the 1mg dexamethasone suppression test, 24-hour urinary free cortisol and/or midnight salivary cortisol.

Pheochromocytoma may be associated with episodic headache, sweating, hypertension and tachycardia. The best screening test is plasma metanephrines.

Adrenal insufficiency is a life-threatening condition with non-specific symptoms. It requires a low threshold of suspicion for evaluation in general practice, particularly in the context of the use of new immune checkpoint inhibitors and before glucocorticoid use.

Congenital adrenal hyperplasia has highly variable presentations and requires the input of a multidisciplinary team of endocrinologists familiar with its complex management.

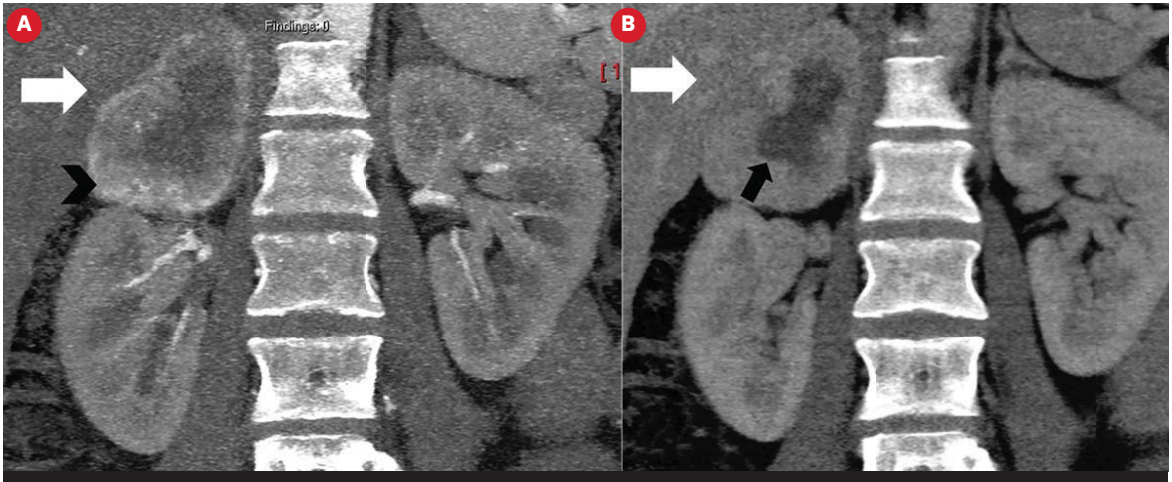

Figure 4. Post-contrast CT of abdomen in arterial phase (A) and portal venous phase (B) in coronal reformats demonstrated a 45mmx60mm pyramidal-appearing mass in the right suprarenal region, representing a phaeochromocytoma (white arrow). It displayed arterial contrast blush (black arrowhead) and had a cystic/necrotic centre (black arrow). No contralateral adrenal mass or calcification was seen.

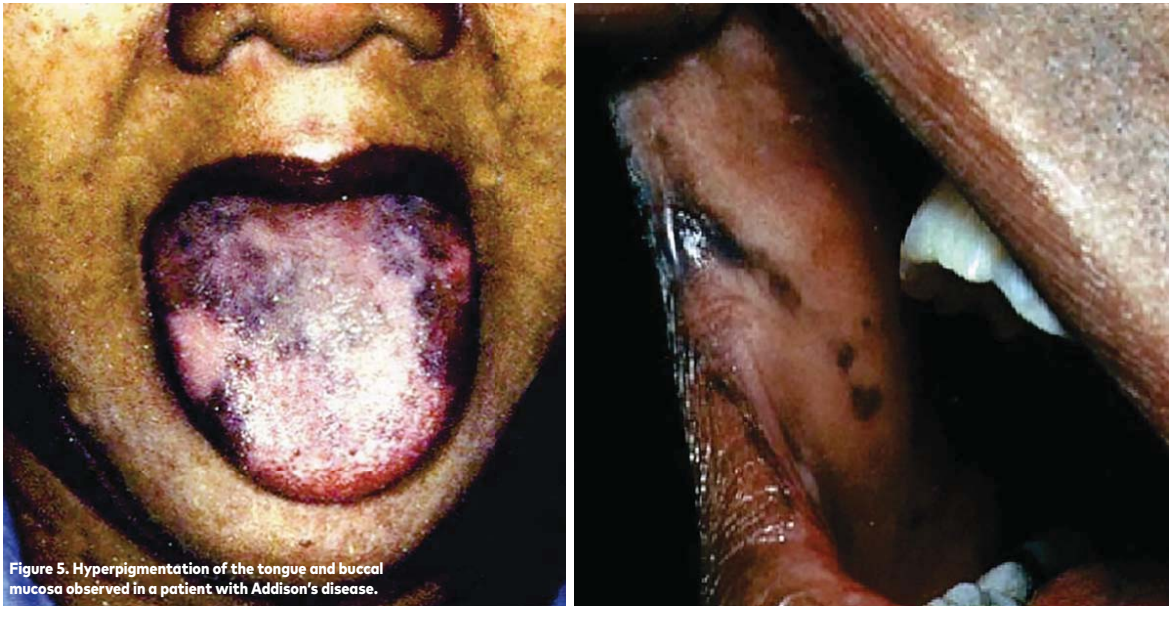

Figure 5. Hyperpigmentation of the tongue and buccal mucosa observed in a patient with Addison's disease.

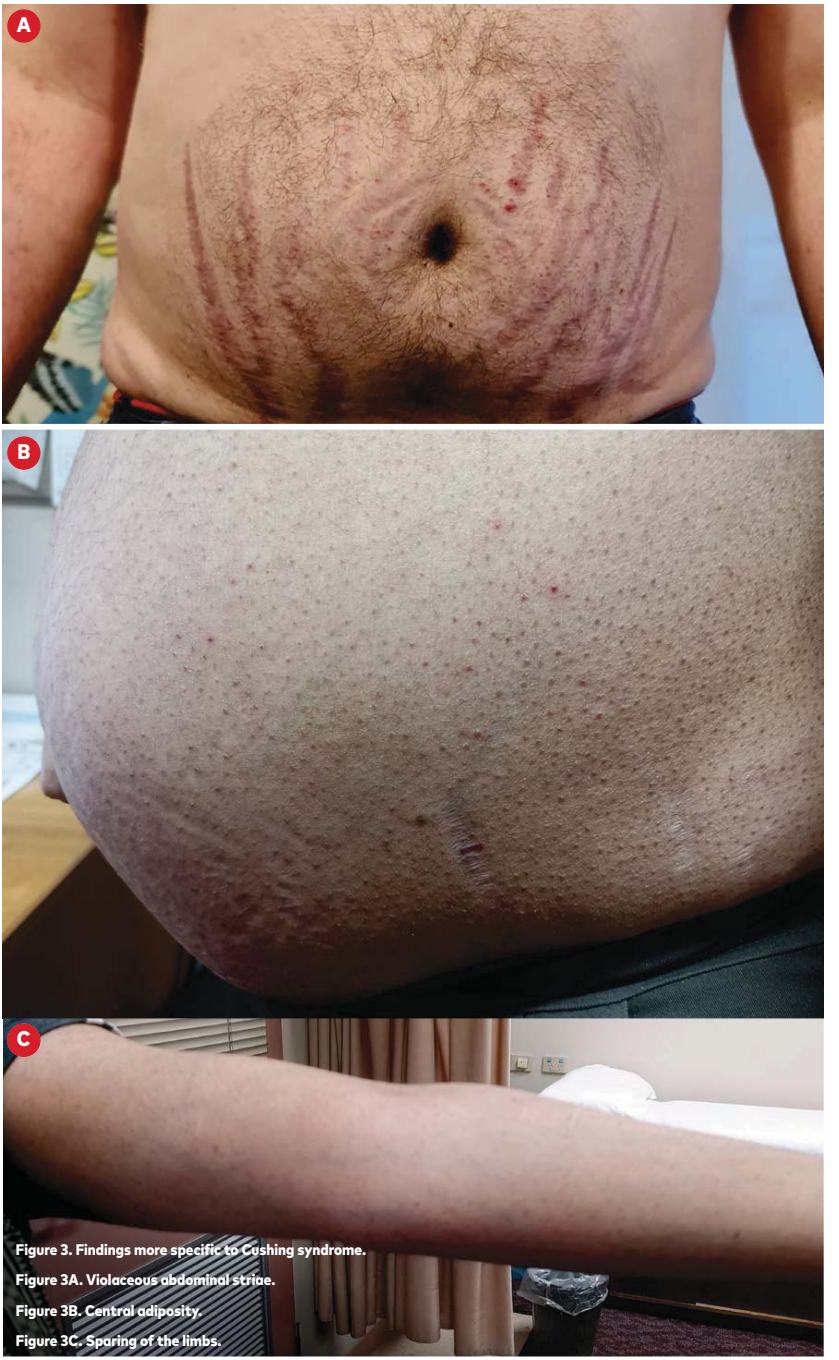

Figure 3. Findings more specific to Cushing syndrome.

Figure 3A. Violaceous abdominal striae.

Figure 3B. Central adiposity.

Figure 3C. Sparing of the limbs.

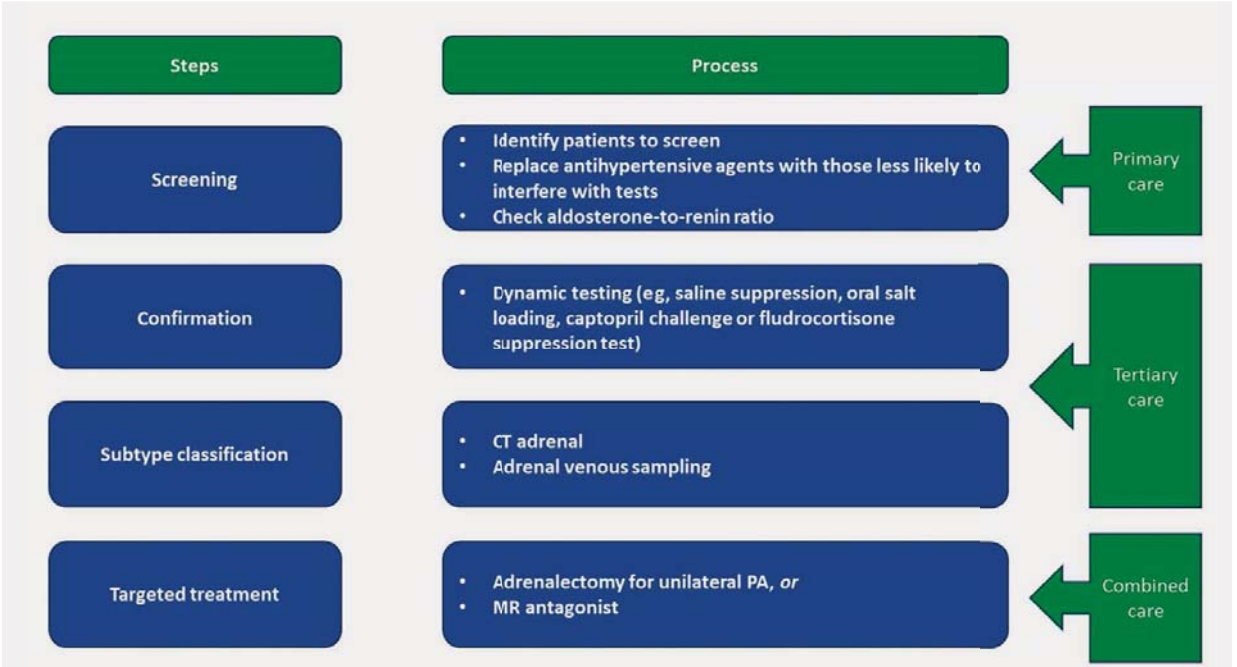

Figure 1. Pathway for the diagnosis and management of primary aldosteronism.

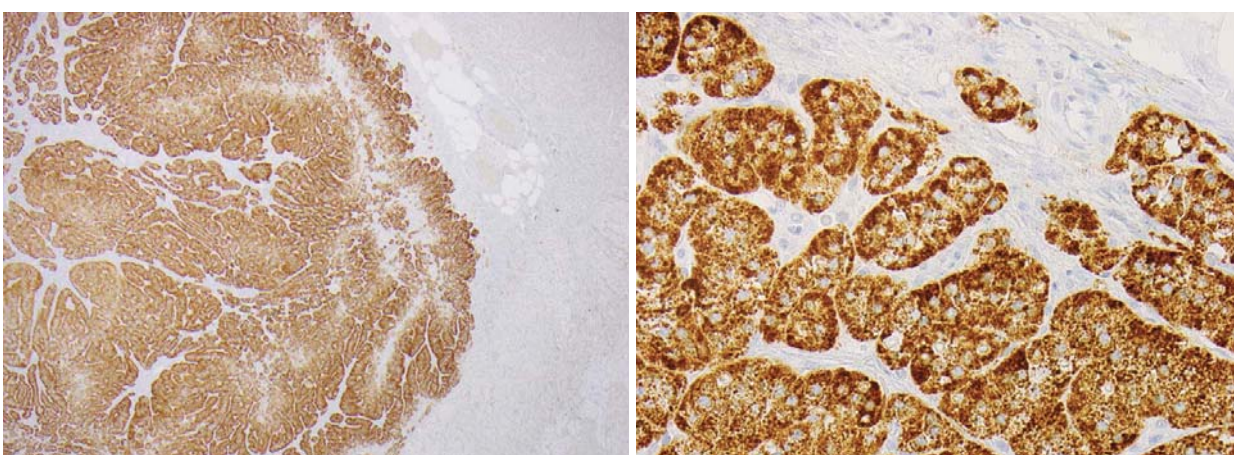

Figure 2. Classic aldosterone-producing adenoma with strong staining for CYP11B2 (aldosterone synthase).

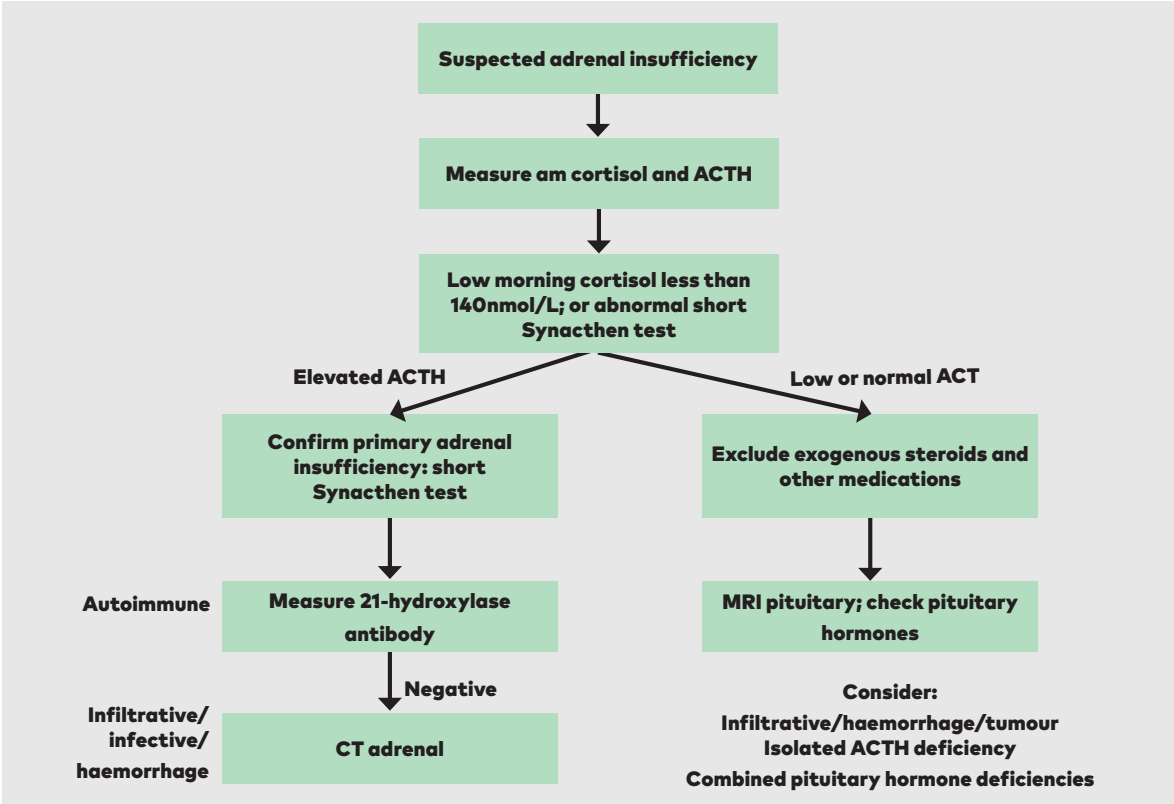

Figure 6. Diagnostic approach to a patient with suspected adrenal insufficiency.

How to Treat Quiz.

ADRENAL DISEASE

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1. **Which THREE statements regarding adrenal incidentalomas are correct?**
   - **a** An incidentaloma is optimally characterised by a dedicated adrenal CT scan.
   - **b** Most of these benign lesions are lipid-rich adenomas.
   - **c** All adrenal incidentalomas require resection because of the high risk of malignancy.
   - **d** For adrenal masses where hypersecretion and/or malignancy is suspected, referral to a multidisciplinary specialist service is appropriate.

2. **Which TWO statements regarding PA are correct?**
   - **a** PA is the most common cause of secondary hypertension.
   - **b** Both unilateral and bilateral PA are treated with an MR antagonist.
   - **c** PA is associated with a higher rate of cardiovascular complications.
   - **d** Screening for PA is based on the saline suppression test.

3. **Which THREE drugs may cause a false-negative ARR?**
   - **a** Beta blocker.
   - **b** Diuretic.
   - **c** ACEI.
   - **d** Angiotensin II receptor blocker.

4. **Which ONE feature is NOT common to both Cushing syndrome and the metabolic syndrome?**
   - **a** Obesity.
   - **b** Diabetes.
   - **c** Easy bruising.
   - **d** Hypertension.

5. **Which THREE are part of the classic triad of symptoms associated with a pheochromocytoma?**
   - **a** Episodic headache.
   - **b** Hypertension.
   - **c** Sweating.
   - **d** Tachycardia.

6. **Which TWO are more specific features of primary adrenal insufficiency?**
   - **a** Salt craving and hyperkalaemia.
   - **b** Fatigue.
   - **c** Weight loss.
   - **d** Hyperpigmentation of the skin and mucous membranes.

7. **Which THREE statements regarding iatrogenic adrenal insufficiency are correct?**
   - **a** Suspect exogenous glucocorticoid exposure in patients with a low cortisol and ACTH but no evidence of hypothalamic–pituitary disease.
   - **b** True adrenal insufficiency may follow the withdrawal of glucocorticoids.
   - **c** Immunotherapies and a range of other medications can cause a low cortisol level via different mechanisms.
   - **d** Hydrocortisone is more likely to suppress ACTH than dexamethasone or betamethasone.

8. **Which ONE best describes adrenal fatigue?**
   - **a** A condition caused by chronic exposure to stressful situations.
   - **b** Adrenal 'overuse' and subsequent failure, leading to fatigue.
   - **c** Not a medical condition that is recognised by endocrinology societies.
   - **d** Fatigue resulting from overuse of the hypothalamic–pituitary–adrenal axis.

9. **Which TWO statements regarding CAH are correct?**
   - **a** Precocious puberty and a tall stature may result from poor control of CAH.
   - **b** The classic type causes primary adrenal insufficiency in children, with virilised genitalia in the female.
   - **c** Females may develop hirsutism, menstrual irregularities and subfertility.
   - **d** Non-classic CAH in adolescent and adults from PCOS are distinguished by measuring cortisol levels.

10. **Which THREE statements regarding the management of CAH are correct?**
    - **a** A higher prevalence of psychiatric and substance abuse disorders has been reported in patients with CAH.
    - **b** In children the focus of management is to allow timely growth and development.
    - **c** Long-acting glucocorticoid is preferred in children as this improves drug adherence.
    - **d** Glucocorticoid and mineralocorticoid replacement are essential in classic CAH.

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