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Adrenal insufficiency – recognition and management

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ABSTRACT

Adrenal insufficiency is characterised by inadequate glucocorticoid production owing to destruction of the adrenal cortex or lack of adrenocorticotropic hormone stimulation. In primary adrenal insufficiency, lack of mineralocorticoids is also a feature. Patients can present with an insidious onset of symptoms, or acutely in adrenal crisis, which requires prompt recognition and treatment. Chronic glucocorticoid therapy is the most common cause of adrenal insufficiency. The diagnosis of adrenal insufficiency is made by demonstrating low basal and/or stimulated serum cortisol and should be followed by appropriate investigations to establish the underlying aetiology. Maintenance glucocorticoid replacement is usually given as a twice or thrice daily hydrocortisone preparation. Patients with primary adrenal insufficiency also require mineralocorticoid. Regular monitoring for features of under- and over- replacement is essential during follow-up. Patient education is a key feature of management of this condition.

Introduction

The adrenal cortex secretes the essential steroid hormones, cortisol and aldosterone, under the control of pituitary adrenocorticotropic hormone (ACTH), angiotensin II and plasma potassium. The most frequent cause of adrenal insufficiency is exogenous steroid use. Up to 2.5% of the population are taking such steroid medications for inflammatory or immune-mediated conditions.[1] These individuals are vulnerable to steroid deficiency if the medication is stopped suddenly. ACTH deficiency (secondary adrenal insufficiency) as a result of pituitary tumours, infiltrative diseases, head injury or congenital hypopituitarism is the next most frequent cause, present in around 1 per 3,000 individuals.[2] High dose opiates, which frequently induce hypogonadotropic hypogonadism, are also increasingly recognised as a cause of hypothalamic-pituitary-adrenal (HPA) suppression.[3] By comparison, primary adrenal insufficiency is rare, with a prevalence of 1 in 8,000 people.[4] In developed nations, an autoimmune attack directed against the adrenal steroidogenic enzymes (predominantly 21-hydroxylase)[5] accounts for about 85% of cases. Around 60% of patients with autoimmune Addison's disease have an additional autoimmune condition, most frequently autoimmune thyroid disease or type 1 diabetes.[6] In developing countries, tuberculosis, disseminated fungal infections and HIV remain significant causes of primary adrenal failure. In primary adrenal insufficiency, secretion of both cortisol and aldosterone is lost, whereas in secondary adrenal failure, or adrenal insufficiency caused by exogenous steroids, aldosterone secretion is largely intact.

Presentation of adrenal insufficiency

The clinical presentation depends on the tempo and extent of the loss of adrenal function. Common features of adrenal insufficiency include weight loss, anorexia, nausea, vomiting, lethargy and fatigue. In primary adrenal failure, features of mineralocorticoid insufficiency – including postural hypotension, muscle cramps, abdominal discomfort and salt craving – are more pronounced. Skin pigmentation, most readily visible on the skin creases and scars, extensor surface of the elbow, knuckles, lips and gingival mucosa, is present in 90% of people with primary adrenal failure. Other features include hypoglycaemia or an unexplained reduction in insulin requirement in an individual with diabetes mellitus[7] and, in

Key points

Symptoms of adrenal insufficiency are non- specific and a high level of clinical suspicion is required to make the correct diagnosis

Patients treated with glucocorticoids for 3 weeks or longer can become adrenally suppressed and abrupt withdrawal of steroids may result in adrenal crisis

Adrenal crisis is a medical emergency and requires immediate treatment with parenteral hydrocortisone and intravenous saline

In patients with primary adrenal insufficiency, mineralocorticoid replacement should be actively tailored to the patient's needs

Continuous patient education is key in allowing patients to have an unrestricted life with minimal disability

KEYWORDS: ACTH, adrenocorticotropic hormone, adrenal insufficiency, glucocorticoid ■

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women, loss of axillary and pubic hair due to lack of adrenal androgen secretion.

Adrenal insufficiency may also present with acute haemodynamic decompensation: hypotension, tachycardia, hypovolaemia (shock) frequently with disorientation or impaired consciousness, known as adrenal crisis. Adrenal crisis often occurs in the context of a major stressor, such as infection or trauma. It can also be a presenting feature of acute cortisol deficiency in cases of bilateral adrenal infarction or haemorrhage, or in pituitary apoplexy. This is a medical emergency and occurs more frequently in individuals with primary adrenal insufficiency because the major precipitant of adrenal crisis is the mineralocorticoid insufficiency resulting in electrolyte and fluid balance disturbance (hence 'adrenal' not 'pituitary' crisis).

Hyponatraemia is present in more than 90% of patients with primary adrenal failure at diagnosis; hyperkalaemia is less frequent (50%). Other laboratory abnormalities include moderate renal impairment, hypercalcaemia or hypoglycaemia, mild normochromic anaemia, eosinophilia and lymphocytosis.[8] Moderate serum thyroid-stimulating hormone (TSH) elevation with normal free thyroxine (T4) is common at presentation and reflects lack of glucocorticoid inhibition on TSH release rather than hypothyroidism.[9] This is important to recognise as commencing thyroid hormone treatment without replacing glucocorticoids can precipitate adrenal crisis. In patients with secondary adrenal insufficiency, electrolyte disturbance is less common and less profound; however, there may be other features of pituitary disease, including hypogonadotropic hypogonadism, central hypothyroidism, hyperprolactinaemia and visual field defects. Importantly, patients with exogenous suppression of the HPA axis ('tertiary adrenal failure') may paradoxically appear Cushingoid, owing to the effects of steroid medication that has been recently withdrawn, leaving a state of functional adrenal failure. Steroid doses equivalent to 7.5 mg of prednisolone taken for 3 weeks or longer can lead to adrenal suppression. However, in people taking medications that reduce steroid metabolism, such as ritonavir or itraconazole (potent CYP3A4 inhibitors), co-administration of even small doses of exogenous steroid (typically inhaled fluticasone) may cause profound HPA axis suppression.[10,11]

Investigating adrenal insufficiency

Doctors are poor at recognising adrenal insufficiency, with two thirds of patients presenting to medical professionals three or more times with symptoms of adrenal failure before the correct diagnosis is made.[12] This highlights the popular adage, '*if you think of adrenal failure: exclude it*'. The diagnostic difficulty lies in the fact that cortisol secretion has a circadian rhythm, so the timing of sampling affects the result and as a 'stress hormone', cortisol secretion depends upon the health state of the patient (eg well and ambulant versus critically ill). Generally, a random serum cortisol of over 400 nmol/L at any time of the day makes adrenal insufficiency highly unlikely,[8] while a morning serum cortisol of less than 100 nmol/L strongly suggests adrenal failure.[13] In interpreting such results, one must consider the patient's current and prior steroid usage, as well as conditions affecting cortisol binding globulin, such as pregnancy or oral estrogen therapy, which can result in falsely reassuring cortisol concentrations.[14] However, when faced by an unwell patient, clinical suspicion is sufficient to institute management with parenteral steroids. The diagnosis can be re-evaluated in 24 or 48 hours.[8] In suspected autoimmune Addison's disease, checking plasma renin and ACTH is useful, as elevation in these hormones is present months to years before serum cortisol becomes abnormal.[15,16] When uncertainty exists as to whether a patient has adrenal insufficiency, a synacthen ($ACTH_{1-24}$ stimulation)[17] test should be used. In this test, 250 µg of synthetic ACTH is given parenterally and serum cortisol is measured 30 and/or 60 minutes later. Each lab should have a prospectively validated serum cortisol threshold for this test; however, cortisol values exceeding 500 or 550 nmol/L are usually deemed to represent a normal response. A synacthen test should not be used to diagnose secondary adrenal insufficiency of recent onset (within 4–6 weeks) – for instance in the context of pituitary apoplexy or recent pituitary surgery – as the adrenal glands might not have become completely atrophic yet.[18] If diagnosed in the acute setting and in the absence of a structural lesion or other aetiological factor, it is worthwhile to revisit the diagnosis of adrenal insufficiency at a later stage. This is easily achieved by measuring 8 am serum cortisol and ACTH after omitting the morning steroid dose.

Aetiology of adrenal failure

As exogenous steroid use is the commonest cause of adrenal insufficiency, careful consideration should be given to the patient's medication history – including oral, injectable, inhaled and topical steroids as well as nutritional and health supplements. Having ruled this out, measurement of plasma ACTH distinguishes between primary and secondary adrenal failure.[8] Autoimmune Addison's disease is present in 85% of European patients with high plasma ACTH[6] and this should be confirmed by measuring serum adrenal or steroid 21-hydroxylase autoantibodies. If these are negative, an adrenal computerised tomography scan should be obtained to rule out tuberculosis, haemorrhage or malignant disorders. In males, measurement of serum very long chain fatty acids identifies those with adrenoleukodystrophy/adrenomyeloneuropathy, an X-linked recessive disorder[8] that can manifest with adrenal insufficiency prior to any obvious neurological deterioration (Fig 1). In the case of a low or normal ACTH, a pituitary magnetic resonance imaging scan should be obtained, along with measurement of anterior pituitary hormones (eg prolactin, luteinising hormone, follicle-stimulating hormone, testosterone or estradiol, TSH, FT4, insulin-like growth factor 1), menstrual history and a visual field check to identify a possible aetiology.

Glucocorticoid replacement

The goal of glucocorticoid replacement in adrenally insufficient patients is to abolish symptoms of glucocorticoid deficiency and prevent adrenal crisis while avoiding over-replacement. The cornerstone of glucocorticoid replacement is oral hydrocortisone, typically 15–25 mg daily, taken in divided doses. Total daily hydrocortisone requirement is dependent on body surface area with normal cortisol production rate about 6 $mg/m^2/day$.[19] The first dose, generally 10 mg, should be taken immediately on wakening.[20,21] A further one or two smaller doses should be taken at 4–6 hourly intervals, with the final dose taken more than 4 hours before bedtime. Typical dose

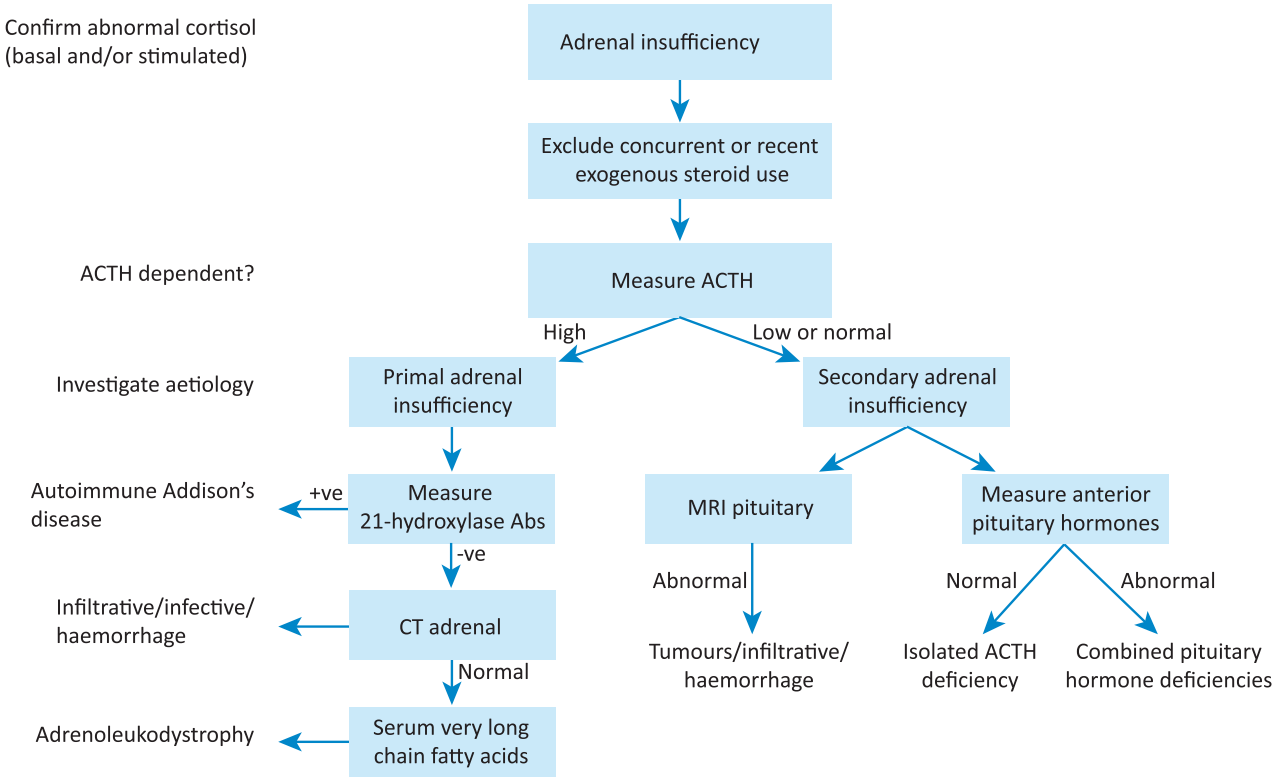

Fig 1. Algorithm for the initial investigation of adrenal insufficiency. +ve = positive; -ve = negative; Abs = antibodies; ACTH = adrenocorticotropic hormone; CT = computerised tomography; MRI = magnetic resonance imaging

regimens should be tailored for body size/weight; however, there is significant inter-individual variability as absorption and disposal kinetics differ. For smaller adults (<65 kg), a regimen of 10 mg on waking and 5 mg between midday and 14:00, or three doses of 10 mg, 5 mg and 2.5 mg taken at 07:00, 12:00 and 16:00, respectively, are suitable. Higher doses of hydrocortisone may be required for larger individuals, but doses greater than 25 mg are rarely necessary, providing that adequate mineralocorticoid replacement is given to patients with primary adrenal failure.

Longer-acting steroids can be used, with a single or twice daily dose of prednisolone (3–5 mg taken once; or 3 mg on waking, 1 mg at midday) especially in those with poor compliance with multiple daily dose regimens. Medications such as dexamethasone, beclomethasone or deflazacort have a long half-life, easily resulting in overtreatment and so should not be used.

None of the current glucocorticoid preparations can exactly mimic physiology and overtreatment with glucocorticoids is a frequent complication. In addition, there are no biochemical parameters that can be used reliably for monitoring of under- or overtreatment. Serum cortisol and ACTH, or 24-hour urinary free cortisol excretion, are a poor reflection of tissue exposure to cortisol during glucocorticoid replacement. In daily practice, clinical judgement is used to assess the adequacy of glucocorticoid doses. Patients should be monitored for weight gain, development of glucose intolerance, moon face, double chin, thin skin, decreased bone mineral density or osteoporotic fractures. Overtreatment with glucocorticoids can lead to increased cardiometabolic risk and possibly increased mortality.[22,23] Conversely, presence of symptoms such as anorexia, weight loss, retching or vomiting, fatigue, breathlessness and persistent or increasing pigmentation (in a patient with primary adrenal failure) indicate insufficient replacement. However, even in the absence of these crude features, fine tuning of glucocorticoid doses is important as even slight glucocorticoid overexposure will increase the risk of complications. A series of 10 helpful questions to use in fine-tuning glucocorticoid replacement is shown in Box 1.[24]

Box 1. Useful questions in assessing timing and total dose of glucocorticoid replacement

- Are you clock-watching for one particular dose?
- Do you often miss a dose because you haven't noticed the time?
- How are your general energy levels/get up and go?
- Do you have low spots during the day?
- Are you napping during the day?
- What time is bedtime?
- Do you sleep okay?
- How do you feel first thing in the morning?
- Changes in weight?
- Changes in pigmentation?

From Napier and Pearce[24]

Mineralocorticoid and sodium replacement

Patients with primary adrenal insufficiency need mineralocorticoid replacement to maintain bodily sodium, fluid balance and blood pressure. Inadequate mineralocorticoid and/or salt intake is among the commonest causes for repeated adrenal crises. Unlike glucocorticoid replacement, patients can omit their mineralocorticoid medication and feel well for several days before the body's sodium reserve is depleted. This can lead to poor compliance, particularly when compared with the almost immediate ill-effects that patients feel after omitting glucocorticoid medication.

Mineralocorticoid replacement is usually taken as a single dose of 50–200 µg of fludrocortisone. However, children, younger adults, pregnant women in the third trimester and very physically active individuals may need significantly higher doses, occasionally up to 500 µg daily. Individuals with primary adrenal failure must be specifically instructed to take salt and sodium-rich foods *ad libitum*, and to ignore healthy eating advice to reduce salt intake applicable to the rest of the population. Insufficient mineralocorticoid replacement can result in postural light-headedness, fainting, nocturia, cravings for salty or sour/acidic foods and, therefore, patients should be asked about any of these during follow-up visits. Assessment of blood pressure, including for postural change, and measurement of serum sodium and potassium should be undertaken regularly. In addition, plasma renin should be measured although this is primarily a marker of plasma volume (renal perfusion) rather than directly of sodium state. In the presence of hypertension, cautious reduction of the fludrocortisone dose can be attempted; however, there is a high probability of adrenal crisis if mineralocorticoid replacement is stopped completely. Initial management of essential hypertension should be with calcium channel blockers or angiotensin-converting-enzyme inhibitors; diuretics should be avoided.

Education for intercurrent illness

Patient education is a key part of the management of adrenal insufficiency and patients need to be empowered to take control of their own medical management, even in the presence of non-expert health professionals.[25,26] A steroid card and medical alert patient identification jewellery are necessary to alert medical personnel in case of unconsciousness. Patients should carry additional hydrocortisone tablets and have a vial of injectable hydrocortisone, needle and syringe available at all times. The affected individual, their partner/spouse and their immediate family members should be trained in parenteral hydrocortisone administration.

During any intercurrent illness, such as a common cold, influenza or infection, that raises the temperature to >37.5°C or makes the person feel systemically unwell, the daily hydrocortisone dosage should be doubled and hydration carefully managed.[8] Two-thirds of adrenal crises and emergency hospital admissions are attributable to gastrointestinal disturbance;[27,28] therefore, patients should be meticulous about doubling hydrocortisone doses if they develop diarrhoea. After a vomiting episode, double the regular oral hydrocortisone dose should be taken immediately, and if there is further vomiting within 30 minutes of this dose then an intramuscular injection of hydrocortisone is warranted.[7] Patient education should be reinforced in the context of acute admission and attempts should be made to identify any missed opportunities that could have prevented adrenal crisis.

Emergency management

Adrenal crisis is a life-threatening emergency that requires immediate recognition and treatment. Approximately 8% of patients with adrenal insufficiency will experience an adrenal crisis each year.[27,28] Gastrointestinal disturbance is the commonest precipitant, but infections, surgical procedures without sufficient steroid cover, accidental injuries, strenuous physical activity, pregnancy and emotional stress are all potential triggers.[29] Once adrenal crisis is recognised, immediate intramuscular or intravenous hydrocortisone 100 mg should be administered, followed by a litre of intravenous 0.9% saline over 30 minutes.[8] Hydrocortisone should continue as intramuscular injections in doses of 50 mg four times a day or 100 mg three times a day; or via intravenous infusion 200 mg/24 hours until the patient is haemodynamically stable, along with additional saline determined by volume status and serum sodium. 50 mg of hydrocortisone has sufficient mineralocorticoid activity to obviate the need for additional fludrocortisone in this situation. Frequently, oral hydrocortisone can be restarted within 12 hours of the admission and the patient may be discharged on a double dose of medication for 48 hours once the precipitating illness is treated and any electrolyte abnormalities are corrected.

New developments

The understanding of the circadian rhythm of cortisol secretion led to development of modified release hydrocortisone preparations that more closely resemble physiology. Plenadren® (Shire Pharmaceuticals) is a dual-release hydrocortisone preparation designed for once daily administration, available in 20 mg and 5 mg doses. Its bioavailability is about 20% less than with conventional hydrocortisone. In a crossover study of 64 individuals with Addison's disease, 12 weeks of Plenadren® therapy resulted in modest improvements in blood pressure and weight reduction compared with an equivalent dose of thrice daily hydrocortisone.[30] Importantly, a number of patients with coexisting diabetes (n=9) showed significant improvements in glycaemic control compared with conventional treatment. Thus far, the cost of this preparation (£8 for a 20 mg tablet) prohibits widespread use within the NHS. In addition, advantages other than patient convenience have not been robustly demonstrated to date. However, data are steadily accumulating to support improved metabolic outcomes[31,32] and the use of Plenadren® is likely to increase. An additional product, Chronocort®, containing microparticulate hydrocortisone with delayed absorption, is also currently in development.[33]

In line with the principle of mimicking the physiological pattern of cortisol secretion is the use of continuous subcutaneous hydrocortisone infusions (CSHI), administered using proprietary insulin pumps. A cross-over study of 33 patients comparing thrice daily oral hydrocortisone and CSHI over 12 weeks has reported higher waking salivary cortisol and better control of overnight ACTH levels during pump therapy.[34] Disease-specific quality

of life was also improved in the infusion group, but there was no difference in anthropometric parameters or blood pressure. The nocturnal decline in plasma glucose was also abrogated,[35] which may be a key advantage for patients with coexisting type 1 diabetes. Use of subcutaneous hydrocortisone could have significant advantages for Addison's disease patients with daytime fluctuations in energy levels on oral medication. However, more data are required to fully evaluate the benefits of this approach and its role in day-to-day practice. ■

Conflicts of interest

SHSP is an investigator for the EU-AIR study, which is sponsored by Shire. AP has no conflicts of interest to declare.

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