Addison's disease: a diagnostic challenge

Introduction

Primary adrenocortical insufficiency (Addison's disease) is a rare disorder in which destruction of the adrenal cortex results in reduced production of glucocorticoid, mineralocorticoid and androgens. Despite being over 150 years since Thomas Addison (1855) first described the clinical and pathological features of adrenal failure the disease remains under-diagnosed, leading to unnecessary morbidity and mortality. Finding adrenal insufficiency in a patient with a previously unknown adrenal disorder is a demanding diagnostic challenge, and the condition is life-threatening if not recognized and treated. However, once diagnosed, simple treatment results in the rapid recovery of a critically ill patient, making this one of the most rewarding diagnoses. This article highlights key features and raises awareness of the condition.

Pathophysiology

The adrenal glands lie at the superior pole of each kidney and are composed of two distinct regions: the cortex and the medulla. Addison's disease occurs as a result of adrenal cortex destruction. The adrenal cortex is made up of three distinct anatomical zones:

- The outer zona glomerulosa, which secretes the mineralocorticoid aldosterone: the main physiological stimulus is through the renin–angiotensin system
- The intermediate zona fasciculata, which secretes cortisol: production is stimulated by adrenocorticotropic hormone (ACTH) produced by the pituitary gland, itself released in response to corticotrophin-releasing hormone
- The inner zona reticularis, which secretes adrenal androgens.

Aetiology

Addison's disease is a rare condition with an estimated prevalence in the developed world of 120 per million – higher than previously estimated (Laureti et al, 1999). It is more common in females than males and typically presents in the third–fifth decade of life (Kong and Jeffcoate, 1994).

When Thomas Addison first described adrenal insufficiency, tuberculosis was by far the commonest cause and, to this day, remains the most prevalent underlying cause in the developing world with adrenal involvement occurring in 5% of patients with active tuberculosis (Lam and Lo, 2001). However, in the western world the commonest cause is an autoimmune adrenalitis, accounting for 80–90% of cases. The adrenal glands have a large reserve, so over 90% of the gland has to be destroyed before symptoms appear. Autoimmune destruction of the adrenal glands may be isolated (40%) or part of a multi-organ process (autoimmune polyendocrine syndrome, 60%). Adrenal autoantibodies can be detected in up to 75% of newly diagnosed cases. The major autoantigen is the adrenal enzyme 21-hydroxylase, but antibodies directed against cholesterol side-chain cleavage and 17-hydroxylase can be detected.

Addison's disease may be part of a polyglandular autoimmune syndrome, of which there are two types. Polyglandular autoimmune syndrome type I occurs in 15% of patients with Addison's disease. It is autosomally recessively inherited, typically presents in childhood and is principally the triad of adrenal insufficiency, hypoparathyroidism and chronic candidiasis. It may also be associated with type 1 diabetes mellitus, hypogonadism, chronic hepatitis, immunoglobulin A deficiency, chronic atopic dermatitis, keratoconjunctivitis, vitiligo or alopecia (Betterle et al, 2002).

Polyglandular autoimmune syndrome type II, also called Schmidt syndrome, is more common and may comprise of Addison's disease, thyroid disease, diabetes mellitus and hypogonadism. The condition has an inherited basis with linkage to the HLA major histocompatibility complex, notably HLA DR3 and DR4. Autoantibodies to 21-hydroxylase are usually present and are predictive for adrenal destruction (Betterle et al, 2002).

Other causes of Addison's disease autoimmune diseases are rare (*Table 1*). *Table 2* shows the causes of secondary adrenocortical insufficiency.

Clinical features

The signs and symptoms of Addison's disease are non-specific, making diagnosis difficult. Over 50% of patients can have signs and symptoms of Addison's disease for more than 1 year before diagnosis. Clinical features are predominantly caused by cortisol deficiency, but deficiencies of aldosterone and androgens will also be present to some extent. The nature of the symptoms depends on the disease course, level of hormone loss and any intercurrent illness.

The main symptoms of chronic adrenal insufficiency are shown in *Table 3*. The gastrointestinal symptoms may indicate an impending crisis. Salt craving may also feature. Psychological symptoms of low mood and irritability are often misdiagnosed as depression, chronic fatigue syndrome or anorexia.

Androgen deficiency can result in loss of libido, dry itchy skin and loss of pubic or axillary hair in women. These are masked in men by testicular testosterone production (Allolio and Arlt, 2002).

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Table 1. Causes of primary adrenal failure

Categories	Diagnoses
Autoimmune	Addison's disease
Infections	Tuberculosis, fungal infections, cytomegalovirus, human immunodeficiency virus
Adrenal infiltration	Metastatic spread, amyloidosis, haemochromatosis
Adrenal haemorrhage	Secondary to septic shock, meningococcal sepsis, antiphospholipid syndrome
Inherited disorders	Adrenoleucodystrophy, familial isolated glucocorticoid deficiency
Bilateral adrenalectomy	Surgery
Drug induced	Ketoconazole, mitotane, etomidate

Table 2. Causes of secondary adrenocortical insufficiency

Exogenous glucocorticoid therapy	
Hypopituitarism	Pituitary tumours
	Pituitary surgery
	Pituitary apoplexy
	Post-partum pituitary infarction
	Pituitary irradiation
	Idiopathic
	Lymphocytic hypophysitis

The nature of the disease means that adrenal function continues to deteriorate for many years so that patients who have had sub-clinical symptoms may suddenly present with a crisis precipitated by intercurrent infection or by stress, such as a surgical operation. Patients with acute adrenal insufficiency (Addisonian crisis) typically present with hypotension or hypovolaemic shock, acute abdominal pain, vomiting and often low grade fever. Symptoms are easily misdiagnosed as an acute abdomen. Children with acute adrenal insufficiency often present with hypoglycaemic seizures or failure to thrive.

Hyperpigmentation of the skin is considered a hallmark of primary adrenal insufficiency and is helpful to distinguish primary from secondary dysfunction. The absence of pigmentation does not exclude the disease, however, as it is absent in up to 8% of patients and has led to delayed diagnoses (Runcie et al, 1986). The pigmentation is seen in sun-exposed areas, recent scars, axillas, nipples, palmar creases, pressure points and mucous membranes. The cause of the pigmentation has long been debated but probably reflects increased melanocyte activity induced by proopiomelanocortin-related peptides, including melanocyte-stimulating hormone.

It is important to look for other signs of autoimmune disease, e.g. vitiligo.

Table 3. Symptoms and signs of adrenal insufficiency

Symptoms	Fatigue and weakness
	Anorexia
	Postural hypotension
	Gastrointestinal symptoms – nausea, vomiting, constipation, abdominal pain, diarrhoea
	Muscle and joint pains
	Low grade fever
	Low mood and irritability
Signs	Hypotension
	Hyperpigmentation
	Vitiligo
	Loss of pubic and axillary hair in females

Diagnosis

Diagnosing Addison's is notoriously difficult; a survey of patients with Addison's disease revealed that 60% had sought medical attention from two or more physicians before the correct diagnosis was considered (Ten et al, 2001). Addison's disease is associated with several biochemical abnormalities (*Table 4*) (Burke, 1985; Paterson et al, 1990; Vasikaran et al, 1994).

Random cortisol measurements

Concentrations of cortisol and ACTH vary throughout the day, excreted in a pulsatile fashion following a pattern of diurnal variation. The diagnostic significance of random samples is therefore limited. However, a sample taken when levels are at their highest (between 07.00am and 09.00am) can provide useful information if interpreted correctly. A cortisol concentration of >500 nmol/litre effectively rules out the possibility of adrenal insufficiency in the majority of cases and a concentration of <100 nmol/litre (especially in a stressed individual) is highly suggestive of the diagnosis (Grinspoon and Biller, 1994). For acutely ill patients with severe sepsis or major insult, there are no agreed limits or cut-off values, but cortisol concentrations of >700 nmol/litre probably rule out adrenal insufficiency (Vermes et al, 1995). Values below this level are doubtful and further dynamic testing is required.

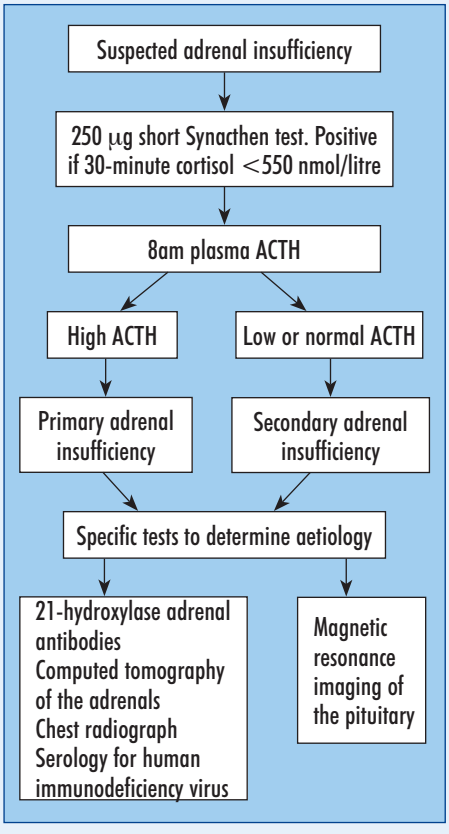
Table 4. Laboratory findings in adrenal insufficiency

	Abnormality	Frequency
Biochemistry	Hyponatraemia	90%
	Hyperkalaemia	60%
	Hyperuricaemia	Depends on hydration status
	Hypoglycaemia	50%
	Hypercalcaemia	5%
Haematology	Normocytic anaemia	
	Neutropenia	
	Eosinophilia	
	Lymphocytosis	

Tetracosactrin (Synacthen) tests

The Synacthen test is used to test adrenal reserve. Synacthen is tetracosactrin, a synthetic analogue of the first 24 amino acids of ACTH. The short Synacthen test is relatively easy to interpret and judges the response to a 250 µg load of Synacthen (*Figure 1*). The test should be done at 09.00am and cortisol is checked before and 30 minutes post administration of Synacthen (Wood et al, 1965). In healthy individuals, the basal plasma cortisol should exceed 170 nmol/litre and rise by 250 nmol/litre to at least 550 nmol/litre. These values vary in different laboratories. The hypoadrenal patient is unable to raise his/her serum cortisol in response to Synacthen (Clark et al, 1998). A blunted

Figure 1. Diagnosis of adrenal insufficiency. ACTH = adrenocorticotropic hormone.



response to Synacthen and a raised ACTH level is diagnostic of Addison's disease.

A depot Synacthen test can also be performed to distinguish between primary and secondary adrenal failure. Depot tetracosactrin (1 mg) is given, and cortisol is measured at 0, 6 and 24 hours. The normal response is peak levels at 4–6 hours (about 900 nmol/litre) and a small further rise within 24 hours. Addison's disease is diagnosed by no rise and secondary failure is diagnosed by suboptimal rise at 4–6 hours with an increased level at 24 hours.

Adrenal autoantibodies

Adrenal cortex autoantibodes or antibodies against 21-hydroxylase are present in more than 80% of patients with recent onset autoimmune adrenalitis (Winqvist et al, 1992).

ACTH

Serum ACTH levels will be high in Addison's disease and low in secondary adrenal insufficiency.

Imaging

Adrenal imaging is not indicated in patients with an unequivocal diagnosis of autoimmune adrenalitis. If infection, haemorrhage, infiltration or neoplastic disease is suspected, abdominal computed tomography scans should be done. In adrenal tuberculosis, bilateral adrenal enlargement is present in the subacute phase with calcification developing during later stages (Sawczuk et al, 1986).

Other tests

Patients with autoimmune Addison's disease should be screened for other autoimmune disease. Autoantibody screening and measurement of calcium, thyroid function tests, glucose and full blood count is necessary. Thyroid function may resemble hypothyroidism but can be reversed with glucocorticoid treatment, known as 'glucocorticoid-reversible hypothyroidism'. Abnormal thyroid function should be rechecked after several weeks on glucocorticoids (Burke, 1992).

Treatment

Emergency treatment

Acute adrenal insufficiency is a medical emergency; treatment should not be delayed pending laboratory results (*Figure 2*). In a critically ill patient with hypovolaemia, a plasma sample for cortisol and ACTH should be obtained, and then treatment with an intravenous bolus of hydrocortisone 100 mg and intravenous saline commenced. The combination of a low serum cortisol (<100 nmol/litre) and elevated plasma ACTH (>100 ng/litre) is diagnostic in these circumstances (Oelkers, 1996). Glucose may also be required and close K+ monitoring needed. If, at a later date, a Synacthen test is required the patient should be converted onto intravenous hydrocortisone or oral dexamethasone which can be stopped for 24 hours before testing.

Long-term treatment

Education of both the patient and the family is one of the most important aspects of the management of chronic primary adrenal insufficiency (*Figure 3*). Patients should understand the need for lifelong replacement therapy, the need to increase the dose of glucocorticoids during minor or major stress, and the need to inject hydrocortisone, methylprednisolone or dexamethasone in emergencies. Patients should carry a steroid card and Medic Alert bracelets should be encouraged. A survey showed that the risk of adrenal crisis was 3.3 per 100 years (Arlt and Allolio, 2003). Most crises were the result of glucocorticoid dose reduction or lack of dose adjustment by patients or clinicians in appropriate circumstances (*Table 5*).

Glucocorticoid replacement

The ideal glucocorticoid replacement therapy should closely mimic normal physiological cortisol release. In practice, this is best achieved with hydrocortisone given at a total dose of about 30 mg daily, with 20 mg in the morning and 10 mg in the afternoon or early evening. Anecdotal data suggests that patients prefer to take the hydrocortisone in three evenly divided doses. Only one study has currently been performed which looks at the benefit of three daily doses, but despite claiming an improvement, there were significant flaws with design and patient selection

Figure 2. Management of acute adrenal crisis.

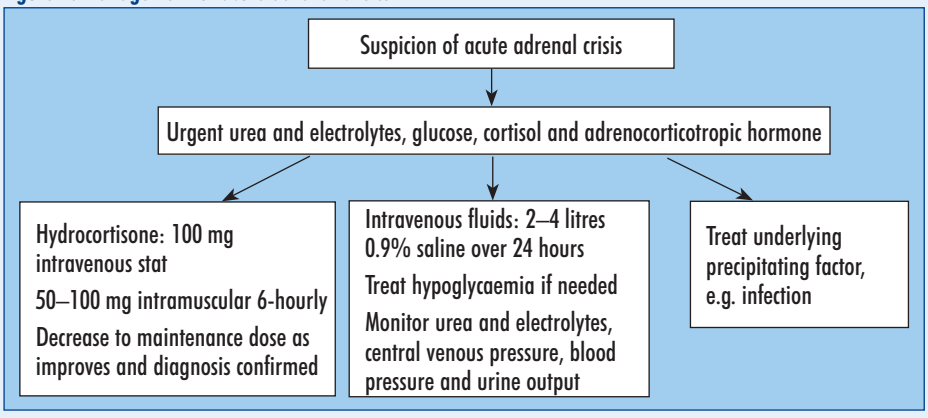


Figure 3. Management of chronic adrenal insufficiency.

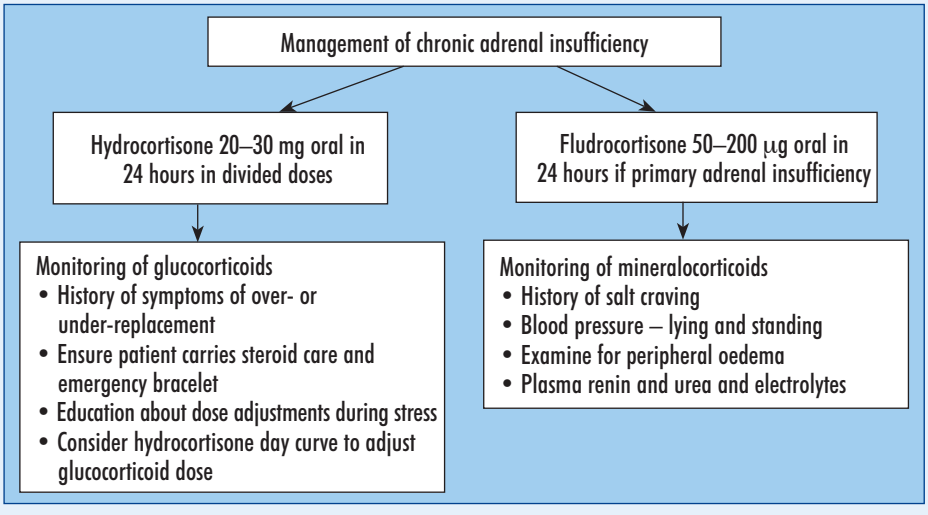


Table 5. Adjustment of glucocorticoid replacement doses

	Examples of activities	Dose alteration
Exceptional activities	Strenuous hike, stressful university exam (but a routine visit to the dentist or sports lesson does not usually require glucocorticoid dose adjustment)	5–10 mg hydrocortisone 1–2 hours before start
Moderate stress	Flu-like infection, surgical procedure with local anaesthesia	Double the usual oral daily dose until recovery (usually within 2–4 days) (in case of prolonged vomiting or diarrhoea seek emergency intravenous or intramuscular injection of hydrocortisone)
Severe stress	Major surgery with general anaesthesia, trauma, delivery	100–150 mg continuously intravenous/24 hours (alternatively 3 x 50 mg intramuscular /24 hours) for 2–4 days, then taper dose and switch to oral administration depending on clinical progress

(Groves et al, 1988). Hydrocortisone should be used as the steroid of choice. Longer half-life steroids such as prednisolone result in high night-time glucocorticoid activity and therefore sleeplessness.

Treatment surveillance of chronic glucocorticoid replacement is mainly based on clinical grounds because no objective assessment has proven to be reliable for monitoring replacement therapy. Clinicians therefore have to rely primarily on clinical judgement, taking into account signs and symptoms potentially suggestive of over-treatment (obesity, impaired glucose tolerance and osteoporosis) or under-treatment (tiredness, low mood and impending crisis).

Osteoporosis is not to be expected with the recommended replacement doses of hydrocortisone (Braatvedt et al, 1999).

Mineralocorticoids

Aldosterone replacement consists of oral fludrocortisone 50–200 μg daily. Fludrocortisone is not required when large doses of hydrocortisone are given because of the mineralocorticoid effect of the latter (20 mg hydro = 0.05 mg fludro) Monitoring therapy depends upon clinical judgement, blood pressure, serum potassium and sodium levels.

Androgens

Replacement of dehydroepiandrosterone does not routinely occur in the UK. However, it has been shown to have positive effects on wellbeing and mood in patients with Addison's disease, predominantly women (Arlt et al, 1999). The exact role these compounds play in management is still not completely clear, but several large scale studies are currently ongoing.

Special circumstances

Hyperthyroidism

Hyperthyroidism increases cortisol clearance. In patients with adrenocortical insufficiency and unresolved hyperthyroidism, glucocorticoid replacement should be increased by two–three times.

Pregnancy

Unless pregnancy is associated with severe nausea and vomiting then no changes to glucocorticoid doses should be needed. Delivery is likely to require higher doses of steroid replacement.

Drug interactions

Treatment of tuberculosis with rifampicin increases cortisol clearance, thus glucocorticoid replacement should be doubled during concomitant rifampicin therapy. BJHM

Conflict of interest: none.

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KEY POINTS

- Addison's disease affects about 120 people per million population but is a master of disguise.
- Autoimmune adrenalitis is the commonest cause of Addison's disease in the western world.
- If the diagnosis is suspected and the patient is very unwell, then treatment should be commenced without delay, confirmation can be obtained at a later date.
- Dynamic testing is the key to diagnosis.
- Patient education is crucial to management and prevention of crises.