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Adrenal insufficiency

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Clin Med 2008;8:211–15

Adrenal insufficiency (AI) is caused by:

- primary adrenal failure due to loss or destruction of the adrenal glands or a block in steroid production (as in congenital adrenal hyperplasia (CAH)) or
- secondary failure (ie impairment of the corticotropic axis in the hypothalamic-pituitary region).

Epidemiology and causes
(Tables 1 and 2)

Five per 10,000 population are affected by AI, three because of hypothalamic-pituitary disease and one each from primary AI and CAH.[1] Suppression of the corticotropic axis due to exogenous glucocorticoid treatment (eg for asthma or rheumatoid arthritis) may affect up to 1% of the UK population and 3% of the elderly. More women than men are affected. Age at manifestation varies but is usually around 20–40 years for autoimmune adrenalitis and 30–60 years in secondary adrenal failure.[1] Most patients suffering from CAH manifest neonatally; AI due to other causes is a rare event in childhood.

Clinical presentation

Adrenal insufficiency represents a continual diagnostic challenge as most signs and symptoms are rather non-specific and may be misleading, resulting in delayed diagnosis. Every second patient is diagnosed only after presentation with an adrenal crisis and most will see more than three doctors prior to diagnosis.

Acute AI (ie life-threatening adrenal crisis) typically presents with severe hypotension or hypovolaemic shock, accompanied by vomiting, nausea, abdominal tension, and in some cases even severe neurological dysfunction including coma. In children, it often

Key Points

Adrenal insufficiency (AI) is either of primary origin, mostly due to autoimmune-mediated destruction of the adrenal gland, or of secondary origin, in most cases caused by tumours located in the hypothalamic-pituitary region affecting the regulatory control of adrenal cortisol release

Common clinical symptoms of AI (fatigue, nausea, weight loss and myalgia) are rather non-specific and may lead to considerable delay in diagnosis. Acute AI is life-threatening and may present with fever, severe hypotension or hypovolaemic shock, abdominal tension and, in some cases, even coma

Diagnostic tests should never delay treatment in cases of suspected acute AI. The short synacthen test is the most suitable tool for establishing the diagnosis of AI; baseline cortisol is of limited value

Therapeutic management of AI always requires cortisol replacement. Monitoring is based on clinical judgment. Mineralocorticoid replacement can be monitored by supine and erect blood pressure, urea and electrolytes, and plasma renin activity. Dehydroepiandrosterone (DHEA) replacement therapy can be a beneficial option, in particular in women with signs of androgen deficiency due to lack of adrenal DHEA production

Recent data indicate significantly impaired well-being, increased rates of disablement, inability to work and mortality. Optimisation of therapeutic strategies in AI are therefore an important target of future research

KEY WORDS: Addison's disease, adrenal insufficiency, aldosterone, cortisol, dehydroepiandrosterone

results in hypoglycaemia that can cause seizures and permanent brain damage.

Chronic AI is associated with fatigue, myalgia, reduced strength and weight loss as a consequence of glucocorticoid deficiency. Mineralocorticoid deficiency manifests with postural hypotension, low sodium and often also increased potassium. Nausea and abdominal pain in adrenal crisis are mainly related to mineralocorticoid deficiency and thus seldom observed in secondary adrenal failure. Lack of the adrenal sex steroid precursor dehydroepiandrosterone (DHEA) in women may result in dry skin, lack of libido and loss of pubic hair.

Diagnosis

The treatment of suspected acute adrenal failure should never be delayed awaiting diagnostic tests. Initial tests should be confined to baseline blood samples (serum cortisol and plasma ACTH), with serum aldosterone, DHEA sulphate (DHEAS) and plasma renin activity (PRA) as optional tests. However, a baseline cortisol is sufficiently diagnostic only if below 50 nmol/l. Mineralocorticoid deficiency in primary AI manifests with low or subnormal aldosterone levels and concurrently increased PRA. Serum DHEAS is usually very low, but of diagnostic value only in younger individuals as DHEAS levels decline with age.

Table 1. Causes of primary adrenal insufficiency (AI).

Diagnosis	Pathogenesis
Isolated autoimmune adrenalitis	Associations with HLA-DR3, CTLA-4
Autoimmune adrenalitis as part of APS:	
• APS type 1 (APECED)	• *AIRE* gene mutations; may include hypoparathyroidism, chronic mucocutaneous candidiasis and other autoimmune disorders
• APS type II	• Associations with HLA-DR3, CTLA-4
Infectious adrenalitis due to:	
• Tuberculosis	• Tuberculous adrenalitis
• AIDS or severe immunosuppression	• Adrenalitis due to HIV-1, CMV, Cryptococcus, histoplasmosis, coccidioidomycosis
Adrenal infiltration	Adrenal metastases, adrenal lymphoma, sarcoidosis, amyloidosis, haematochromatosis
Bilateral adrenalectomy	Unresolved Cushing's, bilateral phaeochromocytoma, bilateral nephrectomy
Bilateral adrenal haemorrhage	Septic shock, meningococcal sepsis, primary antiphospholipid syndrome
Drug-induced AI	Etomidate, ketoconazole, RU-486, mitotane, aminoglutethimide, suramin
Genetic disorders causing primary adrenal failure	
• Adrenoleukodystrophy, adrenomyeloneuropathy	• Mutations of the ABCD-1 gene encoding for the peroxisomal transporter protein ALP
• Congenital adrenal hyperplasia	• Mutations in the genes encoding for 21-hydroxylase (CYP21A2, >90% of cases), 11β-hydroxylase (*CYP11B1*), 17-hydroxylase (*CYP17A1*), P450 oxidoreductase (*POR*) or 3β-hydroxysteroid dehydrogenase type 2 (*HSD3B2*)
• Congenital lipoid hypoplasia	• Mutations in the genes encoding for SrAR and the side chain cleavage enzyme (CYP11A1)
• Other rare genetic causes of primary adrenal failure (*causative gene mutation*)	• X-linked adrenal hypoplasia congenital (*NROB1*), SF-1 linked adrenal hypoplasia congenital (*NR5A1*), IMAge syndrome (*unknown*), familial glucocorticoid deficiency type 1 (*MC2R* encoding for the ACTH receptor) and type 2 (*MRAP*), Triple A syndrome (*AAAS* encoding for ALADIN)

ACTH = adrenocorticotropic hormone; APECED = autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy; APS = autoimmune polyglandular syndrome; CMV = cytomegalovirus; SrAR = steroidogenic acute regulatory protein.

Short synacthen test

The primary diagnostic tool in AI is the short synacthen test (SST) in which blood samples for serum cortisol are drawn before and after administration of 250 µg $ACTH_{1–24}$ (synacthen).[2,3] In the UK, this test is traditionally carried out with blood sampling at baseline and 30 min after intramuscular (im) administration of synacthen, but intravenous (iv) ACTH administration and blood sampling after 60 min is similarly adequate. The accepted cut-off for a sufficient cortisol response is 550 nmol/l. There is significant variability depending on the locally used cortisol assays,[4] so establishing local reference ranges is recommended.

The SST has been shown to have an excellent correlation with the insulin tolerance test (ITT)[2] which is still considered the diagnostic gold standard. However, the ITT is cumbersome, has contraindications (cardiovascular disease, cerebrovascular disorders, diabetes) and is more expensive than the SST. The ITT requires injection of insulin to induce hypoglycaemia below 2.2 mmol/l, blood sampling for serum cortisol and plasma ACTH at 0, 20, 30, 45, 60 and 90 min (normal response peak serum cortisol above 550 nmol/l).

In most instances the SST will be sufficient for diagnosis of AI, with the important exception of the first four weeks after suspected or manifest pituitary insult. Exogenous ACTH stimulation will still elicit an adrenal cortisol response during this period, despite the loss of endogenous ACTH.

Plasma ACTH is significantly raised in primary AI. If adrenal autoantibodies are negative, further investigations should include a chest X-ray to exclude tuber-

culosis (South Asians and Eastern Europeans at greatest risk), and in young men serum levels of very long-chain fatty acids to exclude adrenomyeloneuropathy. In doubt, adrenal imaging by computer tomography should be performed to exclude infiltration or bilateral haemorrhage. Adrenal tuberculosis imposes as bilateral hyperplasia, with calcifications in disease of longer duration. If low levels of plasma ACTH indicate secondary origin of disease, magnetic resonance imaging of the hypothalamic-pituitary region should be undertaken.

Treatment

Glucocorticoid replacement (Table 3)

Replacement of glucocorticoid is usually given in 2–3 daily doses, with one-half to two-thirds administered in the morning. Physiological daily cortisol production rates are 5–10 mg/m^2, which is equivalent to oral administration of 15–25 mg hydrocortisone (= cortisol) or 25–37.5 mg cortisone acetate. The latter requires activation to cortisol by hepatic 11β-hydroxysteroid dehydrogenase type 1. Both preparations result in highly variable peak concentrations within the supraphysiological range followed by a rapid decline to below 100 nmol/l 5–7 hours after ingestion.

It is not clear whether a thrice daily glucocorticoid regimen would be preferable to twice daily as well-designed and appropriately powered studies are lacking. Some groups advocate weight-related dosing.[5] In general, if a twice daily regimen is applied, the second dose should be administered about 6–8 hours after the first.

Long-acting glucocorticoids are also used for replacement (equipotency doses are considered to be 1 mg hydrocortisone = 1.6 mg cortisone acetate = 0.2 mg prednisolone = 0.025–0.05 mg dexamethasone). Prednisolone and dexamethasone have considerably longer biological half-lives which may result in unfavourably high night-time glucocorticoid activity. The glucocorticoid dose needs to be increased in the presence of coincident hyperthyroidism or during treatment with drugs that increase cortisol clearance (eg rifampicin or mitotane).

Monitoring chronic glucocorticoid replacement (Table 3). No objective assessment has proven a reliable tool for monitoring the quality of glucocorticoid replacement, so monitoring is based mainly on clinical grounds.[1] ACTH cannot be used as a criterion for glucocorticoid dose adjustment as in primary AI it is invariably high before the morning dose and rapidly declines with increasing cortisol levels after glucocorticoid ingestion. Aiming at ACTH levels within the normal range would therefore lead to chronic over-replacement. Urinary 24-hour free cortisol excretion has been advocated for monitoring replacement quality,[6] but urinary cortisol excretion shows considerable interindividual variability after exogenous glucocorticoid administration. Also, following glucocorticoid absorption, cortisol-binding globulin (CBG) is rapidly saturated, resulting in transient but pronounced increases in renal cortisol excretion. Thus, reference cannot be made to normal ranges for healthy subjects when judging urinary cortisol excretion during replacement therapy for AI. To measure a random serum cortisol without knowing the exact time of preceding glucocorticoid administration is not helpful in monitoring glucocorticoid replacement.

Some authors have suggested regular measurements of serum cortisol day curves to monitor replacement therapy.[6,7] However, the efficacy of this approach is not supported by controlled studies and recent data indicate a poor correlation between clinical assessment and timed serum cortisol measurements.[8] Importantly, none of the available glucocorticoid preparations can mimic the physiological diurnal cortisol pattern found in healthy subjects due to their pharmacokinetic properties.

Table 2. Causes of secondary adrenal insufficiency (AI).

Diagnosis	Pathogenesis
Pituitary tumours	Generally consequences of growth or treatment of pituitary adenomas; pituitary carcinomas are rare
Other tumours of the hypothalamic-intrasellar or suprasellar metastasis	Craniopharyngioma, meningioma, ependymoma, and pituitary region
Pituitary irradiation	Craniospinal irradiation in leukaemia, brain tumours outside the hypothalamic-pituitary region, hypothalamic-pituitary tumours
Lymphocytic hypophysitis	Mostly isolated and manifesting during or after pregnancy; isolated ACTH deficiency may manifest as part of APS type 2
Sheehan's syndrome	Pituitary apoplexy or necrosis due to hypocirculation of the pituitary due to hypovolaemic or circulatory shock (often manifest after complicated deliveries associated with severe blood loss)
Pituitary infiltration	Tuberculosis, sarcoidosis, histiocytosis X, Wegener's granulomatosis, actinomycosis
Head trauma	Brain concussion, contusion
Genetic disorders (*causative gene*)	*POMC* deficiency syndrome with AI, red hair and early-onset obesity; combined pituitary hormone deficiency with progressive development of panhypopituitarism (pituitary transcription factors including *Pit1, PROP1, POUF-1, T-pit, HESX-1, SOX-9*)
AI due to glucocorticoid-treatment	Suppression of the hypothalamic-pituitary axis due to exogenous administration of 7.5 mg prednisolone equivalent or more for >4 weeks (or due to endogenous Cushing's)

ACTH = adrenocorticotropic hormone; APS = autoimmune polyglandular syndrome; *POMC* = pro-opiomelanocortin.

Thus, in the absence of objective parameters indicating replacement quality, the physician has to rely primarily on clinical judgment, carefully taking into account signs and symptoms potentially suggestive of glucocorticoid over- or under-replacement. The latter carries the risk of incipient crisis and significant impairment of well-being. Conversely, chronic over-replacement may lead to substantial morbidity, including impaired glucose tolerance, obesity and osteoporosis. An increased incidence of osteoporosis has been reported only in AI patients receiving daily replacement hydrocortisone doses 30 mg or higher, so bone mineral density measurements are not required for regular follow-up in AI patients receiving recommended doses.

Important future developments in this area include the development of delayed- and slow-release hydrocortisone preparations with the potential to mimic the physiological circadian rhythm of cortisol secretion.[9]

Mineralocorticoid replacement (Table 3)

Mineralocorticoid regulation via the renin-angiotensin-aldosterone system is still intact in hypopituitarism but replacement with fludrocortisone is usually required in primary AI. Typical doses are 0.05–0.2 mg, with a starting dose of 0.1 mg. Monitoring of mineralocorticoid (Table 3) includes measurement of sitting and erect blood pressure to exclude postural hypotension and serum sodium and potassium. Plasma renin activity should be measured, aiming at the upper normal range of the local reference range. If essential hypertension develops, mineralocorticoid dose may be slightly reduced (but never completely stopped), accompanied by monitoring of serum sodium and potassium.

Glucocorticoids also contribute to the mineralocorticoid pool as they bind to the mineralocorticoid receptor (MCR) with equal affinity to that of aldosterone. However, excessive MCR binding of cortisol in the kidney is prevented by 11β-hydroxysteroid dehydrogenase type 2 which inactivates cortisol to cortisone. A dose of 20 mg hydrocortisone is equivalent to 0.05 mg fludrocortisone in terms of mineralocorticoid potency. Synthetic glucocorticoids have reduced or, in the case of dexamethasone, absent MCR; this needs to be considered when changing replacement from hydrocortisone to a synthetic steroid.

DHEA replacement (Table 3)

Replacement of DHEA has been shown to have significant positive effects on well-being and mood in patients with primary and secondary AI,[10,11] in particular in women in whom it can serve as an elegant tool for androgen replacement. Most women with AI suffer from pronounced androgen deficiency as adrenal DHEA production is the most important androgen source in females. Currently, DHEA replacement is hampered by the lack of pharmaceutically controlled preparations and requires ordering via the international pharmacy and prescription documenting its use outside of a licence. At present, DHEA should be reserved for patients with AI suffering from significant impairment in well-being despite optimised glucocorticoid and mineralocorticoid replacement.

DHEA should be taken as a single dose (25–50 mg) in the morning. Treatment monitoring (Table 3) should include serum DHEAS, in women also androstenedione, testosterone and sex hormone binding globulin, 24 hours after the last morning dose, aiming at the middle normal range for healthy young subjects.

Adrenal crisis

Risk of adrenal crisis is significantly higher in primary AI, in particular in women with polyglandular endocrinopathy and patients over the age of 60.[1]

Table 3. Recommended management strategy in chronic adrenal insufficiency (AI).

Glucocorticoid replacement: hydrocortisone 20–25 mg/d in primary (adrenal) AI and 15–20 mg/d in secondary (hypothalamic-pituitary) AI, administered in 2–3 doses with half to two-thirds of the daily dose in the morning (immediately upon rising)

Monitoring
- detailed history asking for clinical signs and symptoms suggestive of glucocorticoid over- or under-replacement and the ability to cope with daily stress
- detailed account of stress-related glucocorticoid dose self-adjustments since last visit, potential adverse events including emergency treatment and/or hospitalisation
- verification of emergency bracelet/steroid card
- re-instruction regarding stress-related glucocorticoid dose adjustment and emergency guidelines (involve partners/family members)
- body weight

Mineralocorticoid replacement (only in primary AI): fludrocortisone 0.1 (0.05–0.25) mg/d taken as a single dose in the morning

Monitoring
- blood pressure (supine/erect)
- check for peripheral oedema
- serum sodium, serum potassium
- plasma renin activity (target: upper normal reference range)

DHEA replacement (optional): DHEA 25–50 mg/d taken as a single dose in the morning

Monitoring
- serum DHEAS, in women also androstenedione, testosterone, SHBG; blood sampling at trough (24h after last administration), aiming for levels within the normal reference range

Additional monitoring requirements
- *Primary AI due to autoimmune adrenalitis*: serum TSH; in women check for regularity of menstrual cycle
- *Secondary AI*: monitoring of underlying hypothalamic-pituitary disease including replacement of other axes
- Regular follow-up visits in specialised centre (6–12 monthly)

DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulphate; SHBG = sex hormone binding globulin; TSH = thyroid-stimulating hormone.

Many crises are due to glucocorticoid dose reduction or lack of stress-related dose adjustment by patients or general practitioners (GPs).[1]

Prevention

All patients and their family members or carers should receive regular crisis prevention training, including verification of steroid emergency card/bracelet and instruction on stress-related glucocorticoid dose adjustment (Table 3). Preferably all patients, but at least patients travelling or living in areas with limited access to acute medical care, should receive a hydrocortisone emergency self-injection kit (eg 100 mg Solu-Cortef for im injection). Patients should be provided with website details of the Addison Self-Help Group UK (www.addisons.org) which provides useful information, including GP leaflets and emergency guidelines.

In general, hydrocortisone dose should be doubled during infections associated with fever and/or requiring antibiotics until clinical recovery. For major surgery, trauma and diseases requiring intensive care unit monitoring, patients should receive 100–150 mg hydrocortisone/24 hour iv in 5% glucose or 25–50 mg hydrocortisone im qds. Some authors have advocated lower doses (25–75 mg/24 hour) for surgical stress, but studies clarifying exact dose requirements are still lacking.

Management

Management of acute adrenal crisis consists of immediate iv administration of 100 mg hydrocortisone followed by 100–200 mg/24 hour or 50 mg hydrocortisone im qds and continuous infusion of larger volumes of physiological saline solution (initially 1 l/hour) under continuous cardiac monitoring.

Replacement therapy during pregnancy

Pregnancy is physiologically associated with a gradual increase in CBG and, during the third trimester of pregnancy, with a rise in free cortisol. Therefore, hydrocortisone replacement should be increased by 50% during this period. Mineralocorticoids may also require adjustment, due to the antimineralocorticoid action of progesterone. The need should be judged based on sitting and erect blood pressure and serum sodium and potassium levels. In pregnancy, PRA cannot serve as a monitoring tool because it increases physiologically during pregnancy. Peripartal hydrocortisone replacement should follow the requirements for major surgery: 100 mg/24 hour starting with the onset of labour, followed by rapid tapering after delivery.

Quality of life, disablement and prognosis

Mortality is increased in both primary and secondary AI,[12,13] in both situations mainly due to vascular and respiratory disease; the underlying mechanisms are still to be ascertained. Health-related quality of life (QoL) is significantly impaired in AI of both primary and secondary origin.[14,15] The number of patients receiving disablement pensions is about 2–3 times higher than in the general population.[14] The adverse impact of chronic AI on health-related QoL is comparable with that of patients with congestive heart failure, diabetic foot ulcer or on chronic haemodialysis.[14,15] The higher the daily glucocorticoid replacement dose the poorer the QoL,[15] indicating that current replacement strategies require optimisation.

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