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Addison disease

Diagnosis and initial management

Background

Adrenal insufficiency is a rare disease caused by either primary adrenal failure (Addison disease) or by impairment of the hypothalamic-pituitary-adrenal axis. Steroid replacement therapy normalises quality of life, however, adherence can be problematic.

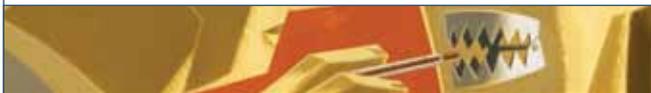
Objective

This article provides information on adrenal insufficiency focusing on awareness of initial symptoms and on risk scenarios, emergency management and baseline investigations, complete investigations and long term management.

Discussion

Early recognition of adrenal insufficiency is essential to avoid associated morbidity and mortality. Initial diagnosis and decision to treat are based on history and physical examination. Appropriate management includes emergency resuscitation and steroid administration. Initial investigations can include sodium, potassium and blood glucose levels. However, complete investigations can be deferred. Specialist advice should be obtained and long term management includes a Team Care Arrangement. For patients, an emergency plan and emergency identification are essential.

Keywords: Addison disease; diagnosis, differential; fludrocortisone; hydrocortisone; patient care planning



Primary adrenal insufficiency was first described by the English physician Thomas Addison in 1855.¹ Addison disease is a rare condition with an estimated prevalence of 4–11 per 100 000 and an incidence of 0.8 per 100 000 population/year.^{2,3} In children, boys constitute approximately 75% of patients in contrast to adults, where the majority (70%) are women.⁴ The underlying pathology is a destruction of the cortex of the adrenal gland.⁵ Secretion of cortisol is reduced or absent, with or without associated reduction or absence of aldosterone. Adrenocorticotropic hormone (ACTH) levels are increased.²

Historically, tuberculosis was the most common cause of Addison disease.^{4,5} Today however, 70–80% of all cases of Addison disease in the Western world are due to autoimmune adrenalitis,^{4,6} whereas worldwide infectious diseases – such as tuberculosis,⁷ fungal infections (histoplasmosis, cryptococcus), and cytomegalovirus – are still important causes. Acute haemorrhage (ie. in meningococcal septicaemia) although uncommon, is also a cause of primary adrenal insufficiency.⁵

Overall, Addison disease in the paediatric population is most commonly attributed to primary adrenal insufficiency, which occurs in approximately one in 15 000 births and usually presents in the neonatal period or early childhood.⁸ Ninety-five percent of cases are due to deficiency of an enzyme (21 hydroxylase) involved in the steroidogenesis pathway, which also results in impaired aldosterone synthesis. In contrast to Addison disease, the adrenal cortex is not destroyed and hence increased ACTH stimulation causes adrenal hyperplasia.⁵

Concomitant autoimmune disease is seen in 50% of patients with Addison disease. These include thyroid disease, hypoparathyroidism and type 1 diabetes mellitus.⁵ More complex associations can be found in two recognised polyglandular autoimmune syndromes (PGA).^{5,8,9}

Secondary forms of adrenal insufficiency, characterised by low ACTH levels, are caused by hypopituitarism due to pituitary disease, or suppression of the hypothalamo-pituitary-adrenal axis (HPA) following steroid therapy or endogenous steroid excess (ie. tumour). The role of inhaled steroids is controversial. It has been suggested that therapy with more than 800 µg/day over a prolonged period of time might result in HPA suppression.¹⁰

In secondary adrenal insufficiency, secretion of aldosterone is not affected. However, with acute hypopituitarism, other hormone



deficiencies including growth hormone, thyroxine, oestradiol or testosterone, must be identified and treated.

When should I consider an adrenal crisis?

Adrenal crisis is a medical emergency and should be considered in any patient presenting with one or more of the following symptoms:

- altered consciousness
- circulatory collapse
- hypoglycaemia
- hyponatraemia
- hyperkalaemia
- seizures
- history of steroid use/withdrawal, or
- any clinical features of Addison disease.

Adrenal crisis may be precipitated by stress, sepsis, dehydration or trauma; clinical features may be modified accordingly. In patients with known adrenal insufficiency, nonadherence with therapy, inappropriate cortisol dose reduction or lack of stress related cortisol dose adjustment can cause adrenal crisis.¹¹

When should I consider Addison disease?

Addison disease can manifest with adrenal crisis. Chronic symptoms result from cortisol deficiency, aldosterone deficiency and excess ACTH:

- cortisol deficiency results in weakness (99%), fatigue, weight loss (97%), anorexia progressing to nausea, vomiting, diarrhoea (20%), constipation (19%), flank or abdominal pain (34%), low blood glucose levels and hyperthermia.^{2,4,5} Fasting hypoglycaemia is common and occurs because of loss of the gluconeogenic effects of cortisol.⁵ In patients with pre-existing type 1 diabetes, deterioration of glycaemic control with recurrent hypoglycaemia can be the presenting sign of adrenal insufficiency²
- aldosterone deficiency causes hyponatraemia, hyperkalaemia, acidosis, tachycardia and hypotension. Low voltage electrocardiogram (ECG) and a small heart on chest X-ray are not necessarily present.^{4,5} Suggestive symptoms are postural hypotension and salt cravings^{2,11}
- excess ACTH is only present in primary adrenal insufficiency. It causes increased melanin production resulting in generalised hyperpigmentation.^{4,5} Because this resembles a suntan, it is essential to inspect areas not exposed to the sun for diffuse hyperpigmentation which can be more obvious in recent scars and in areas such as the axillae, nipples, pressure points, palmar creases, and mucous membranes. Some patients with autoimmune mediated adrenal insufficiency also present with vitiligo.^{2,5}

Chronic unrecognised Addison disease can cause psychiatric symptoms such as memory impairment, confusion, apathy, depression and psychosis.⁵ These features regress on treatment with replacement corticosteroids.

What should I do?

In every scenario the initial diagnosis of acute adrenal insufficiency and decision to treat are based on history, physical examination, and occasionally, laboratory findings (hyponatraemia, hyperkalaemia, hypoglycaemia).¹² Delay in treatment while attempting to confirm this diagnosis can result in poor outcomes and must be avoided (*Table 1*).¹³

Management of adrenal crisis

This is a medical emergency.^{12,13} Acute management is based on emergency resuscitation: restoring and maintaining circulation, administration of IV hydrocortisone, detection and treatment of hypoglycaemia, and identification and treatment of precipitating causes. A specialist should be contacted early. In many cases admission to an intensive care unit will be required.^{12,13}

Management of the subacute or chronic presentation

In most cases patients are cardiovascularly stable. Electrolyte imbalances and hypoglycaemia can be present. Therapy will focus on steroid replacement and fluid resuscitation. Basic laboratory investigations include sodium, potassium and blood glucose levels. Urea, creatinine, calcium and full blood count can be added to specify underlying causes. Referral to an endocrinologist for further investigations will be required to confirm primary adrenal insufficiency. Optional investigations are: serum cortisol, serum ACTH and 24 hour urinary cortisol. If considered necessary, a synacthen (ACTH stimulation) test can be performed but this should never result in delayed administration of steroids and should only be performed under controlled circumstances in the hospital setting.

Education of the patient, and their family, on the diagnosis, importance of adherence, and an emergency management plan must be initiated.

Long term management

Long term management may include a Team Care Arrangement involving a general practitioner, endocrinologist and clinical nurse specialist. Assistance by social workers and psychologists can be important. Medical management includes replacement of cortisol ± aldosterone. Regular specialist reviews are needed to optimise therapy.^{12,14–16} These include: assessment of growth and pubertal development, looking for clinical signs of adrenal insufficiency, biochemical analyses of electrolytes, cortisol levels and, depending on the underlying pathology, ACTH, and monitoring for other autoimmune conditions.⁵ Emphasis will be on the importance of adherence with medication and adjustments for illness and stress situations to achieve a good quality of life.^{11,13} As steroid replacement therapy is associated with an increased risk of osteoporosis, further investigations including dual energy X-ray absorptiometry scans and preventive strategies such as adequate dietary calcium, exercise and vitamin D/sun exposure should be considered.



Emergency plan

An up-to-date emergency plan and practical teaching in administering emergency medication are of paramount importance. At each consultation the physician must ensure that the patient and carer(s) are well versed in the emergency plan and that their ready-to-use vial of emergency hydrocortisone is in-date and available for use at any time.^{11,14} In growing children, the dose may require adjustment and a new appropriate prescription should be issued where indicated. It is recommended that patients wear a MedicAlert bracelet or pendant and have ambulance cover.

Case study 1 – An acute presentation

Paramedics attended a boy, aged 21 months, at his home. His Glasgow Coma Scale was 8/15. He was poorly perfused, with SpO₂ of 76% and capillary blood glucose <2 mmol/L. He had been unwell at home with symptoms of an upper respiratory tract infection for the previous 24 hours. He was given oral glucose gel and IM glucagon with no effect. On arrival at the hospital emergency department he had spontaneous respirations with a heart rate of 126 bpm and cool peripheries. Investigations showed a metabolic acidosis, blood glucose level (BGL) of 1.6 mmol/L, sodium 134 mmol/L and potassium

5.5 mmol/L. He was given a bolus of 10% dextrose followed by normal saline. He then had a generalised tonic clonic seizure, was treated with anticonvulsants and intubated, ventilated and transferred to the intensive care unit. In his background history he had an admission at 11 months of age with profound hypoglycaemia (BGL 0.6 mmol/L) following an episode of gastroenteritis. He had presented to the ED unresponsive and pale following 18 hours of profuse, watery diarrhoea and vomiting. At that time, sodium was recorded at 126 mmol/L with potassium 4.3 mmol/L. He became alert and interactive after 10% dextrose bolus. On the second admission, the boy was noted to have hyperpigmentation of the buccal mucosa (*Figure 1*) and appeared diffusely suntanned. Plasma cortisol was <30 mmol/L with a raised ACTH of 492 pmol/L (normal range 2.0–10). A diagnosis of acute Addisonian crisis was made and he was treated with 50 mg IV hydrocortisone 4 hourly. He made a full recovery. He was discharged on oral maintenance hydrocortisone with an emergency plan. A MedicAlert bracelet and ambulance cover were organised. Further investigations revealed normal aldosterone levels, negative adrenal

Table 1. Summary of the management and prevention of acute adrenal insufficiency^{5,11,14}

<p>Clinical findings</p> <ul style="list-style-type: none"> • Cortisol deficiency: weakness, anorexia, nausea and/or vomiting, hypoglycaemia, hypotension (particularly postural) and shock • Aldosterone deficiency: dehydration, hyperkalaemia, hyponatraemia, acidosis, low blood pressure <p>Investigations</p> <ul style="list-style-type: none"> • Blood sugar level; serum glucose, urea, sodium and potassium; blood gas analysis • Keep extra blood for analysis of ACTH and cortisol if possible • Do not wait for results to start therapy <p>Intravenous fluids</p> <ul style="list-style-type: none"> • Initial fluid resuscitation: NaCl 0.9% 20 mL/kg (severe dehydration); 10 mL/kg (moderate dehydration) – repeat until circulation restored • Maintenance fluids: 5–10% dextrose <p>Steroid replacement (hydrocortisone)</p> <ul style="list-style-type: none"> • If intravenous (IV) access is difficult, give intramuscularly (IM) while establishing IV line • Neonates (1 year): 25 mg stat, then 10–25 mg 4–6 hourly • Toddlers (1–3 years): 25–50 mg stat, then 25–50 mg 4–6 hourly • Children (4–12 years): 50–75 mg stat, then 50–75 mg 4–6 hourly • Adolescents and adults: 100–150 mg stat, then 100 mg 4–6 hourly 	<p>Correction of hypoglycaemia</p> <ul style="list-style-type: none"> • Neonates or infants: 10% dextrose 5 mL/kg (IV bolus) • Older children, adolescents and adults: 25% dextrose 2 mL/kg (IV bolus) <p>Correction of hyperkalaemia</p> <ul style="list-style-type: none"> • Potassium usually normalises with fluid and electrolyte replacement • If K⁺ >6 mmol/L – perform ECG and apply cardiac monitor as arrhythmias and cardiac arrest may occur <p>Identify and treat potential precipitating causes</p> <ul style="list-style-type: none"> • Admit to appropriate inpatient facility <p>When patient tolerates oral intake</p> <ul style="list-style-type: none"> • Reduce IV hydrocortisone dose, then switch to triple dose oral hydrocortisone therapy, gradually reducing to maintenance levels (10–15 mg/m²/day) • Patients with aldosterone deficiency: start fludrocortisone at maintenance doses (usually 0.1 mg/day)¹¹ <p>Prevention</p> <ul style="list-style-type: none"> • Emergency plan for susceptible patients, emergency identification (MedicAlert) • Triple normal oral maintenance dose for 2–3 days during stress (ie. fever, fracture) • Administer IM hydrocortisone if oral medication not tolerated (eg. vomiting) • Increase parenteral hydrocortisone (1–2 mg/kg) before anaesthesia, consider increased dose postoperatively • Ensure patients have ambulance cover and ready-to-use IM hydrocortisone preparation (Act-o-vial®) for emergencies
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antibodies and normal, very long chain fatty acids (to exclude adrenoleukodystrophy). Investigations to exclude other endocrinopathies were normal, and no cause for Addison disease identified.

Ongoing management

Ongoing management in this boy includes oral hydrocortisone maintenance treatment and growth monitoring. An emergency plan with instructions to increase his dose of hydrocortisone in the event of illness is in place. In the event of unresponsiveness or persistent vomiting his parents have been instructed on the administration of IM hydrocortisone and to call the emergency numbers listed on the emergency plan. The importance of adherence with regular medications is reiterated and the boy's emergency plan reviewed at each clinic attendance.



Figure 1. Hyperpigmentation of the buccal mucosa

Case study 2 – Issues in management

A girl, 15 years of age, with a diagnosis of Addison disease made 3 years previously (anti-adrenal antibodies positive) attended her routine endocrinology clinic appointment with her father. She had a history of poor adherence. Regular medications were: prednisolone 4 mg morning and evening and fludrocortisone 100 µg/day. She denied missing her medications. She had regular menses. She described fair energy levels.

On examination she looked well but appeared diffusely suntanned, not confined to, but more obvious in sun exposed areas. Her BP was normal. Records showed that she had not gained weight for the past year.

The patient was intermittently living between her parents' homes. On review of her emergency plan she was unsure of what to do should she become unwell. Her father appeared to be well informed in the management of any illness, however it was revealed that the ready-to-use IM hydrocortisone was only available at her mother's house. New prescriptions for IM hydrocortisone were issued for both homes and for school, and copies of the emergency plan were also made. The importance of adherence with regular medication was reiterated.

Why is Addison disease easily missed?

Addison disease is easily missed due to nonspecific symptoms and presentations, rarity of the condition, and low index of suspicion.

The consequences of delayed diagnosis and treatment are increased morbidity, mortality and medicolegal risk.^{12,13} Outcomes may be improved with a higher index of diagnostic suspicion, prompt emergency management with IM or IV hydrocortisone as indicated, early referral, and good patient education.^{11,13}

Key points in management

- Physical findings are subtle and nonspecific; hyperpigmentation may be seen, particularly in sun exposed areas or pressure points.
- Circulatory compromise can range from mild signs of sodium and volume depletion to shock.
- If in doubt give oral/IM/IV hydrocortisone.
- Don't delay treatment while awaiting laboratory results.

Authors

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