

Diagnosing Addison's: a guide for GPs

Addison's disease (hypoadrenalism) is a rare, potentially fatal condition where the adrenal glands cease to function. Life-long treatment with replacement steroid hormones is required.



With the right balance of daily medication, people with Addison's can expect to have a normal life span and to lead full and productive lives. It is not unknown for people with Addison's to live into their 90s. The most famous Addison's patient was US President John F Kennedy.

THIS LEAFLET OUTLINES THE ROLE OF THE GP IN THE EARLY DETECTION OF ADRENAL FAILURE.

SYMPTOMS AND CLINICAL SIGNS

As well as overwhelming exhaustion, patients with adrenal failure typically report weight loss, loss of appetite and dizziness on standing. Nausea, muscle weakness with cramps, abdominal, joint or back pains are often present. A preference for salty foods and increased thirst are common.

Key signs are deepening skin pigmentation, low blood pressure and a drop in blood pressure on standing (*postural hypotension*). Symptoms reported by patients are shown in the chart below. As this identifies, few patients report the full complement of symptoms. Psychosis is occasionally documented; minor depression and tearfulness may be observed accompanying chronic exhaustion.

GP ROLE IN URGENT ADMISSIONS

Where the patient shows signs of adrenal crisis - typically, persistent vomiting with profound muscle weakness, hypotension, headache, extreme sleepiness or even coma - the patient should be admitted to hospital as an emergency and if possible stabilised by a saline infusion (*for volume repletion*) prior to transfer.

If admission is delayed for any reason or if the patient is *in extremis* with strong clinical suspicion of hypoadrenalism, then consider a 100mg hydrocortisone injection before transportation to hospital.

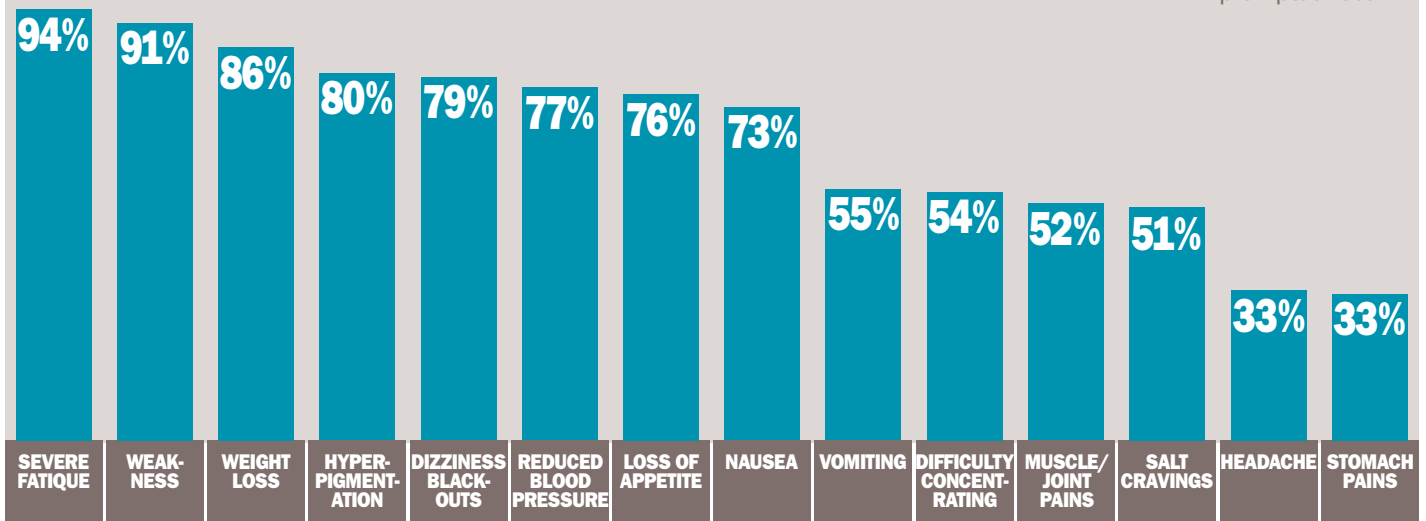
GP ROLE IN PATIENT SCREENING

Where the patient is stable, the GP should assess for clinical signs, especially:

1. Measurement of blood pressure sitting and standing. Postural hypotension usually results in a 20 mmHg drop in blood pressure on standing.
2. Questioning of the patient to establish if they struggle to climb stairs, get up from a sitting/squatting position or carry weights such as the grocery shopping. (*Proximal myopathy or global muscle weakness*).
3. Inspection for patchy hyperpigmentation or, in Caucasians, unusual pigmentation of the palmar creases (*not present in all cases*). Hyperpigmentation generally occurs in areas of increased friction and may be visible where clothes rub against the skin or on the oral mucosa, depending on the patient's natural level of melanocytes.

ADDISON'S SYMPTOMS AT DIAGNOSIS

■ Autoimmune Addisons N = 614 prompted recall



PRIMARY CARE INVESTIGATIONS

Initial laboratory investigations can be carried out in primary care. These are:

1. Electrolytes (low Na, high K)

■ Electrolytes may be borderline/normal where the patient is not in crisis.

2. Blood glucose

■ Blood glucose may be borderline/low, especially in adrenal insufficiency of pituitary origin.

3. 9am cortisol

■ The diagnosis is highly likely if 9am cortisol is less than 100nmol/L - unless the patient is already on oral or inhaled steroids.

■ The diagnosis is unlikely if cortisol is greater than 400 nmol/L - but not excluded if the patient is acutely unwell at the time.

■ For values between 100 and 400 nmol/L the diagnosis can only be excluded by a short Synacthen test (*ACTH stimulation test*). Patients in the early stages of disease may have 9am cortisol values towards the top of this range.

REFERRAL TO A SECONDARY SPECIALIST

Whenever there is a real suspicion of adrenal insufficiency, the GP is encouraged to refer the patient to a specialist endocrinology unit for a Synacthen (*ACTH stimulation*) test. The urgency of this referral will depend on the clinical context. If the patient is hypotensive and vomiting, or where the 9am cortisol is less than 100 nmol/L, an immediate and urgent referral is required.

Associated investigations may include:

■ Plasma renin (*must be drawn at the processing lab*)

■ Plasma ACTH

■ Serum DHEA-S

■ Thyroid function tests

■ Organ-specific antibodies

■ Where pituitary involvement is suspected, further investigations of the hypothalamic-pituitary-adrenal axis may be necessary.

THE DIFFERENTIAL DIAGNOSIS

Some of the early signs overlap with type 1 diabetes, although in adrenal failure the blood glucose should be normal or even low. Excessive fatigue and sleepiness, increased thirst and urination, unexplained weight loss are common to both conditions.

In early stage autoimmune (*primary*) adrenal disease, the predominant signs are usually those of mineralocorticoid deficiency (*postural dizziness, increasing thirst and urination, salt cravings*). Increasing pigmentation is due to elevated pituitary ACTH, as a consequence of HPA feedback from declining glucocorticoid levels.

In early stage pituitary disease, signs of glucocorticoid deficiency will predominate, notably anorexia, weight loss and muscle weakness. Hypoglycaemia may be present in children, but skin pigmentation usually remains unchanged or displays an alabaster-like pallor.

Adrenal destruction triggered by disseminated infections such as tuberculosis, fungal infection or histoplasmosis is more common in regions such as the Indian subcontinent and Latin America; mucocutaneous hyperpigmentation is more frequently observed here. HIV is a growing cause of adrenal failure.

ASSOCIATED ENDOCRINE CONDITIONS

Hypothyroidism occurs alongside autoimmune Addison's in over 40% of patients, although one usually predates the other. Where they develop simultaneously, commencing thyroid replacement without glucocorticoid therapy may precipitate hypoadrenal symptoms and adrenal crisis, as thyroid hormone increases the metabolic rate and breakdown of residual cortisol.

Elevated TSH may be an indicator of hypoadrenalism in an ill patient with extreme fatigue but without the typical features of hypothyroidism. It may return to normal with steroid replacement.

Diabetes (*type 1 or 2*) occurs alongside autoimmune Addison's in around 10% of cases. In established diabetes, a marked reduction in the insulin requirement can be a warning sign of developing hypoadrenalism.

POTENTIAL PITFALLS

■ Random (*untimed*) serum cortisol has a low sensitivity for Addison's disease, especially where the patient is in the early stages of adrenal failure. If you think of the diagnosis on clinical grounds then it is worth referring for a Synacthen test, unless a 9am cortisol is over 400 nmol/L.

■ The slowly progressive nature of adrenal failure means many patients are wrongly identified as depressive or anorexic until intercurrent infection precipitates an adrenal crisis. Around one-third of patients report being told that their symptoms were "all psychological" prior to diagnosis. Some anti-depressants are sodium-depleting and may precipitate adrenal crisis in patients with undiagnosed adrenal insufficiency.

■ Symptoms of hypocortisolaemia or adrenal crisis, in which nausea and vomiting are predominant features, are frequently attributed to gastric infection. One-third of Addison's patients report receiving hospital treatment for adrenal crisis on one or more occasions prior to their diagnosis, without their condition being identified.

■ In pregnancy, Addison's symptoms may be mistaken for hyperemesis and chloasma. Pregnancy, oral contraceptive or HRT usage make interpretation of serum cortisol difficult due to elevation of background CBG and delayed hepatic clearance.

■ Exogenous steroid usage for conditions such as mouth ulcer has been documented to mask underlying adrenal insufficiency.

WORST OUTCOMES IF MISSED

Untreated Addison's disease is universally fatal and the patient may die quite rapidly from adrenal crisis.

In adrenal crisis, hypovolaemic shock, cardiac arrest, stroke or other circulatory complications can occur even in young, fit patients; complications from hypoxia may leave the patient permanently disabled. Children with adrenal crisis are particularly susceptible to hypoglycaemia, which can cause permanent brain damage if not quickly reversed.

Where the patient has severe hyponatraemia, correction can lead to cerebral oedema or central pontine myelinolysis.

EPIDEMIOLOGY

Autoimmune Addison's disease affects about one in 10,000 individuals, with an upper estimate of around 8,400 diagnosed cases in the UK. In common with other autoimmune and inflammatory diseases (*type 1 diabetes, asthma*), there is evidence of increasing incidence in westernised societies. Diagnosis can occur at any age, from 5 to 80. Almost half of all diagnoses occur outside the most common age of onset (30 - 50 years).

KEY QUESTIONS FOR THE GP

1. Does this patient have postural hypotension?

2. Is this patient losing weight without trying?

3. Does this patient have low/borderline blood sodium?

4. Does this patient have salt, soy sauce or liquorice cravings, or increased thirst and urination?

5. Does this patient have appropriate pigmentation; has there been a change in skin colour?

GP FOLLOW-UP

Thorough patient education and training is required to ensure that:

1. All patients know how to adjust their replacement steroid medication for illness, injury or strenuous exercise
2. The patient and a partner are competent to administer an IM injection of 100mg hydrocortisone in emergencies and are fully supplied with needles, syringes and injectable hydrocortisone sodium phosphate (*Efcortisol*)
3. The patient understands the need to wear medical emergency jewellery, preferably a MedicAlert bracelet.

A	= ALWAYS TIRED	(94%)
D	= DIZZY WHEN STANDING	(79%)
D	= DROP IN BLOOD PRESSURE ON STANDING	(77%)
I	= INEXPLICABLE WEIGHT LOSS	(86%)
S	= SKIN COLOUR CHANGES	(80%)
O	= ONLY EATING SPARINGLY/ANOREXIA	(76%)
N	= NO STRENGTH IN HANDGRIP OR LIMBS	(91%)
S	= SICK OR NAUSEOUS	(73%)

FURTHER READING

Artl W, Allolio B, Adrenal insufficiency, **Lancet 2003**; 361 (9372): 1881-93

On-line endocrinology textbook: www.endotext.org/adrenal

Parker K and Kovacs W, 'Addison's disease (adrenal insufficiency)' in Wass JAH, Shalet SM, **Oxford Textbook of Endocrinology and Diabetes**, OUP 2002, 837-844

Online case reports of adrenal insufficiency diagnosis: www.endocrine-abstracts.org

Further information for GPs and their patients can be obtained from the Addison's Disease Self-Help Group at www.addisons.org.uk

THIS LEAFLET OUTLINES THE ROLE OF THE GP IN THE EARLY DETECTION OF ADRENAL FAILURE.

This leaflet has been prepared by the **Addison's Clinical Advisory Panel (ACAP)**:
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ACAP has also issued clinical guidelines for emergency treatment of hypoadrenalism, glucocorticoid medication for surgery and dentistry, and regular GP care for the diagnosed patient. These are available from the ADSHG at www.addisons.org.uk

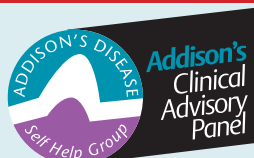
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For further information about the work of the Addison's Disease Self-Help Group, to join the group or make a donation, please visit our website at www.addisons.org.uk

The Addison's Disease Self-Help Group works to support people with adrenal failure and to promote better medical understanding of this rare condition. Registered charity 1106791.

www.addisons.org.uk



The Addison's Clinical Advisory Panel is a group of endocrinologists with an interest in adrenal medicine. It advises the Addison's Disease Self-Help Group on medical matters.

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