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**Practice** Easily Missed?

## Addison's disease

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### Case scenario

A 34 year old woman presented with a 12 month history of increasing tiredness, anorexia, weight loss, and depression. During that period, she had tried two different antidepressant tablets without benefit. She saw her general practitioner's locum, who thought she looked tanned. Her blood pressure was 90/60 mm Hg, although it had always tended to be low. Her serum sodium concentration was 130 (normal range 135-145) mmol/l and potassium concentration was 5.7 (normal range 3.5-5.5) mmol/l. A short Synacthen (tetracosactide) test showed an inadequate serum cortisol response, which together with raised plasma adrenocorticotrophic hormone confirmed the diagnosis of Addison's disease.

## What is Addison's disease?

Addison's disease (also known as primary adrenal insufficiency) is a chronic disorder of the adrenal cortex resulting in inadequate secretion of glucocorticoid and mineralocorticoid. The commonest cause of Addison's disease in developed countries is autoimmune disorder and in developing countries is tuberculosis.<sup>1</sup>

### How common is Addison's disease?

- Addison's disease has a prevalence of 93-140 per million people and an annual incidence of 4.7-6.2 per million people in Western populations.<sup>1 2</sup> A recent epidemiological study suggests that the incidence of Addison's disease is rising<sup>2</sup>
- A survey of patients with Addison's disease found that 60% had seen two or more clinicians before

the diagnosis of Addison's disease was ever considered<sup>3</sup>

- An observational study of children with Addison's disease found that a delay in diagnosis occurred in about a third of the cases, in whom the median duration between the onset of first symptoms and the correct diagnosis was two years<sup>4</sup>

## Why is it missed?

The onset of Addison's disease is often insidious. Its usual symptoms (such as fatigue, lethargy, weakness, and low mood) are non-specific, are highly prevalent in the general population, and overlap with many other common conditions.

## Why does this matter?

A patient with untreated Addison's disease becomes progressively unwell with a markedly reduced quality of life.<sup>5</sup> If Addison's disease is not suspected, such a patient is often misdiagnosed as having other conditions such as depression, chronic fatigue syndrome, anorexia nervosa, or gastrointestinal disorders, leading to unnecessary investigations and inappropriate treatments. Moreover, the patient is at risk of developing serious acute adrenal crisis during an intercurrent illness or stress. Acute adrenal crisis, if not recognised and treated urgently, could be fatal.<sup>6</sup>

## How is it diagnosed?

### Clinical features

A high index of suspicion is required for the diagnosis of Addison's disease. Doctors need to be alert to the possibility of Addison's disease. A cluster of common symptoms, although non-specific in themselves, may point to Addison's disease. A cohort study of 108 patients with Addison's disease found that they had all experienced fatigue, weakness, anorexia, and unintentional weight loss.<sup>7</sup> Other symptoms included gastrointestinal complaints such as nausea and vague abdominal pain (56%), postural dizziness (12%), and musculoskeletal pains (6%).<sup>7</sup> Hyperpigmentation of skin and mucous membranes is a characteristic feature of Addison's disease; however, it is absent in about 10% of cases, which may delay diagnosis.<sup>7 8</sup> Postural hypotension is common in Addison's disease; however, low blood pressure without a postural drop can also occur.

Autoimmune Addison's disease is associated with other autoimmune conditions. For example, vitiligo often coexists with Addison's disease.<sup>7</sup> It is important to consider Addison's disease if a patient with type 1 diabetes starts developing unexplained recurrent hypoglycaemia or the patient's insulin requirement falls as this may signal adrenal insufficiency.<sup>9</sup> Likewise, worsening of symptoms in a patient with autoimmune hypothyroidism after the start of thyroxine treatment should also raise the suspicion of Addison's disease as thyroxine replacement in a patient with untreated Addison's disease can precipitate an adrenal crisis.<sup>10</sup>

About half of patients with Addison's disease are diagnosed only after an acute adrenal crisis.<sup>1</sup> It is a medical emergency often precipitated by an infection or other forms of stress in an undiagnosed or inadequately treated patient with Addison's disease. In this condition, patients present acutely unwell with severe dehydration, hypotension, or circulatory shock.

### Investigations

On routine blood tests, unexplained electrolyte disturbances such as hyponatraemia and hyperkalaemia

may provide a clue to the diagnosis of Addison's disease. Other biochemical abnormalities, including raised urea concentration, hypoglycaemia, hypercalcaemia, and raised concentrations of serum thyroid stimulating hormone, may be present.

A clinical suspicion of Addison's disease must be confirmed biochemically by demonstrating inadequate cortisol production. Owing to the pulsatile nature and diurnal variation of cortisol secretion, random measurement of serum cortisol concentration is inadequate to assess adrenal function in most cases. A short Synacthen test is the investigation of choice to confirm or exclude Addison's disease; it is a safe test, which can be done either in primary care by a general practitioner or in secondary care via referral. In the test, 250 µg of tetracosactide (an analogue of corticotropin) is injected intramuscularly or intravenously, and blood samples for serum cortisol are taken immediately, at 30 minutes, and at 60 minutes. A rise in serum cortisol level to above 500 nmol/l 30 minutes or 60 minutes after the tetracosactide injection is considered a normal response,<sup>1</sup> although this threshold cortisol concentration indicating a normal response may vary according to the reference ranges of local laboratory assays. If the cortisol response to tetracosactide is inadequate, patients should be referred to secondary care for further evaluation and management. A plasma adrenocorticotrophic hormone concentration should be measured as a raised concentration will distinguish Addison's disease from secondary adrenal insufficiency. Plasma renin activity is raised in Addison's disease, and its measurement is also sometimes useful in differentiating between Addison's disease and secondary adrenal insufficiency. Once the diagnosis of Addison's disease is made, further investigations are needed to determine the underlying cause.

## How is it managed?

Addison's disease requires lifelong replacement of glucocorticoid (usually hydrocortisone) and mineralocorticoid (fludrocortisone). The usual replacement dose of hydrocortisone is 15-25 mg a day, given in two or three divided doses.<sup>1</sup> Fludrocortisone is given in a single dose of 50-200 µg a day. During intercurrent illnesses and other forms of stress, patients should double or triple the replacement dose of hydrocortisone; this should be given parenterally if a patient cannot tolerate the drug orally (for example, during repeated vomiting). A patient with an acute adrenal crisis needs urgent hospital admission for intravenous fluid, parenteral hydrocortisone, and treatment of the precipitating cause (for example, antibiotics for infection). If acute adrenal crisis is suspected in an undiagnosed patient, the treatment must not be delayed to carry out investigations.

### Key points

- Common symptoms of Addison's disease such as fatigue, nausea, anorexia, weight loss, and depression are non-specific, and a high index of suspicion is required for the diagnosis
- Addison's disease should be considered in all patients with persistent non-specific symptoms plus hyperpigmentation, unexplained hypotension (sitting or postural), electrolyte disturbance (hyponatraemia and/or hyperkalaemia), or a history of other autoimmune disorders
- A short Synacthen (tetracosactide) test is the key investigation to diagnose or exclude Addison's disease
- If acute adrenal crisis is suspected in an undiagnosed patient, the glucocorticoid replacement must not be delayed to carry out diagnostic tests

## Notes

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## Footnotes

- [doi:10.1136/bmj.b2384](https://doi.org/10.1136/bmj.b2384)
- This is a series of occasional articles highlighting conditions that may be commoner than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. If you would like to suggest a topic for this series please email us ([easilymissed.bmj@bmjgroup.com](mailto:easilymissed.bmj@bmjgroup.com))
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- Patient consent: Patient consent not required (patient anonymised, dead, or hypothetical).

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