Addison's disease

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Abstract

Addison's disease or primary adrenocortical failure is a rare condition, most commonly caused in the UK by autoimmune destruction of the adrenal glands. The insidious onset of symptoms over many months means there is often a delay in diagnosis and patients can first present in adrenal crisis, which is life-threatening if not appropriately treated. The diagnosis is made by the finding of a low serum cortisol at 09:00 hours in the presence of an elevated adrenocorticotrophic hormone (ACTH) concentration, or by a suboptimal cortisol response to exogenous ACTH on provocation testing. Replacement with hydrocortisone and fludrocortisone should approximate physiological concentrations as closely as possible. Patients and family should have a good understanding of their condition and how to adjust corticosteroid dosing in times of illness.

Keywords Addison's disease; adrenal; autoimmune; dehydroepiandrosterone; fludrocortisone; hydrocortisone; MRCP; tuberculosis

Key points

- Addison's disease is associated with a 2-fold increase in mortality
- Replacement doses of glucocorticoid have generally been lower in recent years to minimize exposure to excessive glucocorticoid. This can be given as once-daily, dual-release replacement if compliance with multiple daily dosing is problematic
- A persistent deficit in quality of life is seen despite optimal glucocorticoid and mineralocorticoid replacement; this is sometimes helped by additional androgen treatment, usually as dehydroepiandrosterone. Patient education and regular refreshment about 'sick day rules' is critical to prevent adrenal crisis
- Patients have a 60% risk of developing a further autoimmune disease, so annual clinical review is important

Introduction

Addison's disease (AD), first described by Thomas Addison (1855), denotes primary adrenocortical failure. Most of the original cases described were caused by tuberculosis (TB), but the most common aetiology in the UK is now autoimmunity. AD remains rare; the prevalence is about 120 per million population. A delay in diagnosis is common because of failure to recognize the insidious onset of symptoms; a survey from the US National Adrenal Disease Foundation revealed that 60% of patients with AD had sought medical attention from two or more physicians before the diagnosis was considered.

Anatomy and pathophysiology

The adrenals are Y-shaped glands (each limb measuring <5 mm) located at the superior poles of the kidneys. They comprise a cortex (90%) surrounding a medulla (10%) (Figure 1). The cortex secretes:

- the glucocorticoid cortisol from the zona fasciculata
- androgens (e.g. dehydroepiandrosterone (DHEA)) from the zona reticularis.
- mineralocorticoids (aldosterone) from the zona glomerulosa, predominantly under the control of the renin–angiotensin system (although 5–10% of total aldosterone production is mediated by adrenocorticotrophic hormone (ACTH)).

AD involves all three zones of the adrenal cortex. Overt symptoms do not usually appear until >90% of the gland has been destroyed. Concentrations of glucocorticoids, mineralocorticoids and androgens are reduced, in contrast to the situation in secondary adrenal failure (ACTH deficiency), in which mineralocorticoid secretion is relatively preserved. Immune destruction leads to fibrosis with a mononuclear cell infiltrate, occasional plasma cells and, rarely, germinal centres.

Aetiology

In developed countries, about 75–80% of cases of AD are caused by autoimmune destruction; TB is the second most common cause. Other causes are rare (Table 1). In young females, an autoimmune basis is most likely (three times more common than in males), and there is a higher risk of developing autoimmune AD if the individual was born in winter. Patients with autoimmune AD have a 50–60% risk of developing another autoimmune disorder (10% of patients develop type 1 diabetes mellitus). There is an association with human leukocyte antigen (HLA) DR3 and HLA DR4.

An emerging rare cause of adrenal insufficiency is autoimmune adrenalitis associated with immune checkpoint inhibitors (inhibitors of cytotoxic T lymphocyte associated antigen 4 and programmed cell death 1), used in metastatic cancers such as melanoma. This can occur along with other immune-mediated complications such as hypophysitis, colitis and thyroiditis.[1] Although adrenal metastases are relatively common, hormonal insufficiency is unusual.

Clinical features

Patients can present with an insidious onset of non-specific symptoms (Table 2) or during an adrenal crisis, depending on

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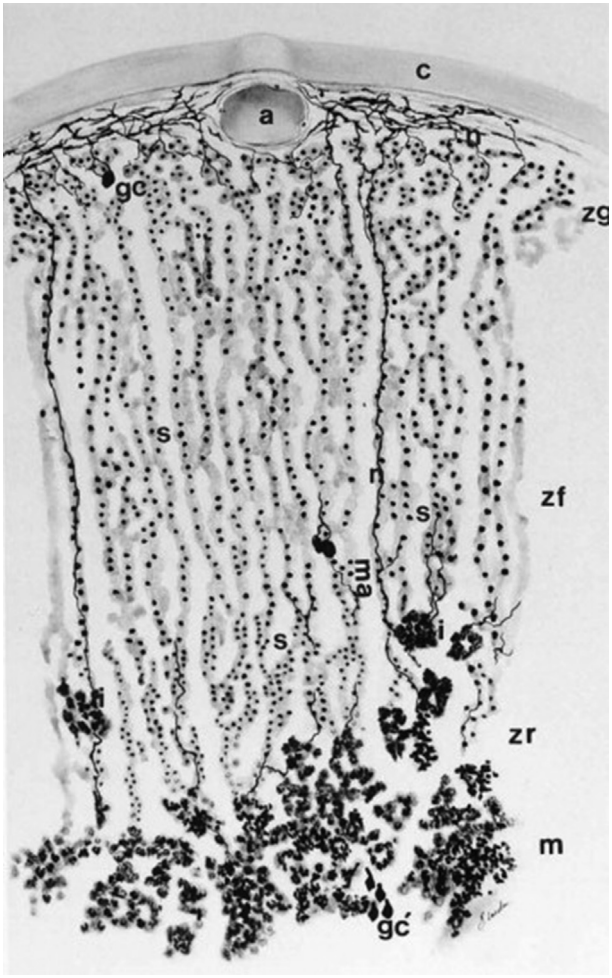

Figure 1 Cross-section of the adrenal gland. a, arteriole; c, capsule; gc, ganglionic cells; i, isolated islets of chromaffin cells; m, medulla; ma, medullary artery; n, nerve fibres; s, sinusoids; zf, zona fasciculata; zg, zona glomerulosa; zr, zona reticularis.

the acuteness of the hormonal deficit and any intercurrent illness. Primary adrenal failure is suggested by hyperpigmentation (consequent on elevation of melanocyte-stimulating hormone and ACTH) in the buccal mucosa, nail beds and areas exposed to light and pressure.

Investigations and diagnosis

Biochemical abnormalities

At presentation, patients are often hyponatraemic, hyperkalaemic and acidotic. Mineralocorticoid deficiency leads to sodium depletion, reduced extracellular fluid volume and hypotension, and results in a raised plasma renin concentration. This can precede cortisol deficiency by several years. Reduced renal water clearance compounds the hyponatraemia. Hyperkalaemia develops as a result of reduced renal potassium and hydrogen ion excretion, and type IV renal tubular acidosis ensues. Low plasma glucose (as a result of reduced glycogen stores) is common, although severe hypoglycaemia is rare in adults. Reversible hypercalcaemia can occur.

Causes of primary adrenal deficiency

Adrenal destruction

Autoimmune

- Isolated
- Autoimmune polyglandular syndrome 1 (autosomal recessive, equally common in males and females, chronic mucocutaneous candidiasis, acquired hypoparathyroidism (90%), AD (60%))
- Autoimmune polyglandular syndrome 2 (autosomal recessive, autosomal dominant and polygenic, more common in females, AD (100%), autoimmune disease of the thyroid (Schmidt's syndrome), immune-mediated diabetes mellitus (Carpenter's syndrome), pernicious anaemia)
- Immune checkpoint inhibitors

Infections

- TB
- Fungal (*Histoplasma, Cryptococcus*)
- Opportunistic (cytomegalovirus in acquired immunodeficiency syndrome)

Metastases

- Lung, breast, kidney, melanoma
- Lymphoma

Haemorrhage

- Waterhouse–Friderichsen syndrome (meningococcal septicaemia)

Infiltrations

- Amyloidosis, haemochromatosis

Others

- Adrenoleucodystrophy

Adrenal dysgenesis

- Congenital adrenal hypoplasia
- Mutations in *SF1*

Impaired steroidogenesis

- Congenital adrenal hyperplasia

Mitochondrial disorders

Iatrogenic

- Adrenal suppressors (e.g. ketoconazole, etomidate)
- Enzyme inducers (e.g. phenytoin, rifampicin)

Table 1

Serum cortisol

The diagnosis is made by documenting low (or within reference range) serum cortisol in the presence of elevated plasma ACTH. A serum cortisol <100 nmol/litre at 09:00 hours is diagnostic of deficiency, and a serum cortisol >550 nmol/litre makes the diagnosis unlikely, although it does not exclude it with certainty (because of assay-dependent ranges). As cortisol secretion is pulsatile, a random cortisol concentration later in the day is rarely diagnostic.

Tetracosactide test

The diagnosis is confirmed by a suboptimal cortisol response to synthetic ACTH. Tetracosactide (Synacthen®), 250 μg intramuscularly (i.m.) or intravenously (i.v.), is given at 09:00 hours, and serum cortisol measured at 0, 30 (or 60) mins. A normal response is a peak >550 nmol/litre at 30 or 60 mins; however, the diagnostic value is assay-dependent, and false-negative results are occasionally obtained.

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