Cushing's syndrome

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Abstract

Endogenous Cushing's syndrome results from prolonged, excessive, inappropriate concentrations of circulating cortisol. Cushing's syndrome should be considered in patients with unusual features for age, patients with multiple and progressive features, children with decreasing height percentile and increasing weight, and patients with adrenal adenoma found incidentally. Endogenous Cushing's syndrome is more common in women than men. Adrenocorticotrophic hormone (ACTH)-dependent causes account for about 80% of cases. Of ACTH-dependent cases, 80% result from pituitary adenomas (Cushing's disease) and the remainder from ectopic ACTH secretion. Non-ACTH-dependent Cushing's syndrome is caused by benign adrenal adenomas in 60% and carcinomas in 40%. Specialist assessment and treatment warrants referral to major centres. For diagnosis, the most discriminating clinical features are thin skin, easy bruising and proximal myopathy. Biochemical diagnosis is by a combination of low-dose dexamethasone suppression tests, assessment of loss of circadian rhythm and urinary free cortisol. When differentiating pituitary and non-pituitary sources of ACTH, reliance should be placed on biochemical evaluation. Medical therapy is often used preoperatively to lower plasma cortisol, postoperatively to control concentrations in patients not cured, and after radiotherapy. Trans-sphenoidal surgery is the treatment of choice for Cushing's disease; laparoscopic bilateral adrenalectomy can be used in refractory cases.

Keywords Adrenal; adrenocorticotrophic hormone; cortisol; Cushing's syndrome/disease; dexamethasone; ectopic; MRCP; pituitary

Key points

- A diagnosis of Cushing's syndrome must be established before any attempt is made to consider a differential diagnosis for the cause
- Cushing's disease (adrenocorticotrophic hormone-dependent Cushing's syndrome caused by a pituitary gland corticotroph tumour) is the most common cause
- Surgical excision of the tumour causing the endogenous Cushing's syndrome is the mainstay of therapy
- Underlying molecular mechanisms of adrenal and pituitary causes of Cushing's syndrome have been delineated
- The number of medical treatments is increasing
- International guidelines summarize approaches to diagnosis and treatment

Introduction

Cushing's syndrome is challenging, and it is recommended that early referral be made to an endocrine centre familiar with all the inherent pitfalls of diagnosis and management.

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Definitions and epidemiology

Cushing's syndrome results from prolonged and inappropriate exposure to excessive circulating free glucocorticoid – cortisol in endogenous Cushing's syndrome.[1] The incidence of Cushing's syndrome is quoted as 1/250,000, with no specific geographical variation, but is likely to be higher as patients are increasingly found with milder disease.

Aetiology

Endogenous Cushing's syndrome is more common in women than men; adrenocorticotrophic hormone (ACTH)-dependent causes account for about 80% of cases. Of ACTH-dependent cases, 80% are caused by a pituitary adenoma (termed Cushing's disease) and the remainder by ectopic ACTH secretion, mainly as a consequence of neuroendocrine tumours, particularly bronchial. Cushing's disease is the cause in 90% of women.[1,2]

ACTH-independent Cushing's syndrome is caused by benign adrenal adenoma in 60% of cases and carcinoma in 40%. Very rare adrenal causes are bilateral primary pigmented nodular hyperplasia (isolated or part of Carney complex), macronodular adrenal hyperplasia, ectopic actions of G-protein-coupled receptors (e.g. gastric-inhibitory peptide receptor, β-adrenergic receptor), and McCune–Albright syndrome. Somatic mutations in the catalytic subunit of protein kinase A,[3] and in the deubiquitinase gene *USP8*,[4] cause adrenal and pituitary Cushing's in around 40–50% of cases, respectively.

Clinical features

Patients often have a history of symptoms lasting 1–2 years before confirmation of the diagnosis (Table 1). The signs that most reliably distinguish Cushing's syndrome are thin skin, easy bruising and proximal myopathy. It is *essential* to exclude

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Clinical features of Cushing's syndrome

- Obesity
- Moon facies
- Hypertension
- 'Buffalo hump'
- Thin skin[a]
- Hirsutism
- Oligomenorrhoea/amenorrhoea
- Purple striae
- Impaired glucose tolerance/diabetes mellitus
- Proximal muscle atrophy[a]
- Psychiatric disturbance
- Osteoporosis
- Bruising[a]
- Acne
- Hypokalaemia

[a] Most discriminating features.

Table 1

exogenous glucocorticoids as the cause of a 'Cushingoid appearance'.

Who to test?

Testing for Cushing's syndrome is indicated in patients with unusual features for their age (e.g. osteoporosis and livid striae in young men) (Figure 1), patients with multiple and progressive features, children with decreasing height percentile and increasing weight, and patients with adrenal adenoma found incidentally on computed tomography (CT) scans performed for other reasons.[2]

Diagnosis

Diagnosis of Cushing's syndrome is a two-step process (Figure 2). It is essential that the diagnosis be confirmed before attempting to determine the cause (see below). Acute intercurrent illness causes hypercortisolaemia and false-positive results for the diagnosis of Cushing's syndrome. For unknown reasons, some patients with Cushing's syndrome exhibit cyclical secretion of cortisol, which can fluctuate and remit spontaneously, sometimes over many years. This can cause considerable diagnostic difficulty, and reinvestigation at intervals and on several occasions may be required.

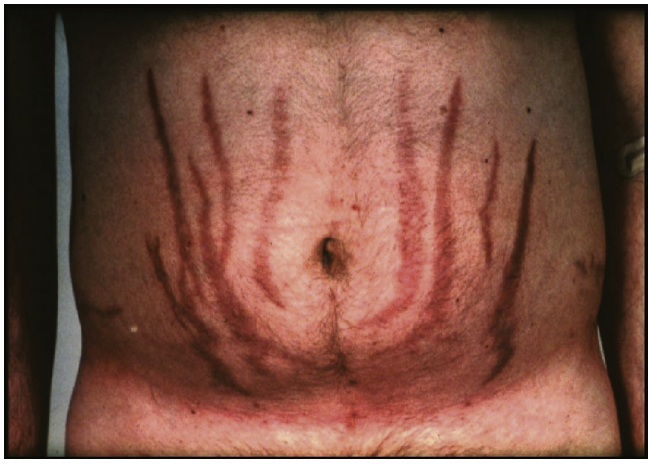

Figure 1 Striae in Cushing's syndrome.

Oral oestrogens increase cortisol-binding globulin and therefore lead to falsely elevated serum cortisol concentration; they should be stopped for 6 weeks before investigation.

Diagnosis of Cushing's syndrome

Three principal tests are commonly used to establish the diagnosis (Figure 2):[1,2]

- low-dose dexamethasone suppression test
- late-night salivary or midnight serum cortisol
- 24-hour urinary free cortisol.

At least two different concordantly abnormal tests are needed to establish the diagnosis.

Low-dose dexamethasone suppression test: two tests are in common use:

- 1 mg overnight (dexamethasone, 1 mg, is given at 11:00 hours and serum cortisol measured at 09:00 hours the next day)
- 48-hour test (dexamethasone, 0.5 mg, is given at 09:00 hours, 15:00 hours, 21:00 hours and 03:00 hours, and serum cortisol measured at 09:00 hours at the start and end of the test)

In healthy subjects, serum cortisol is <50 nmol/litre (1.8 micrograms/dl) following either test. Both tests can give false-positive results if patients are taking drugs that increase hepatic clearance of dexamethasone, including carbamazepine, phenytoin, phenobarbital and rifampicin. Five per cent of patients with Cushing's disease show serum cortisol suppression to <50 nmol/litre; therefore, if the clinical index of suspicion is high, re-testing and use of other tests is advised.

Assessment of loss of circadian rhythm of salivary or serum cortisol: the normal circadian rhythm of cortisol secretion is lost in Cushing's syndrome. Late-night salivary cortisol is a useful screening test and can be performed in the community. Use of liquid chromatography tandem mass spectrometry (LC-MS/MS) is recommended. Sleeping midnight serum cortisol concentration is also used for this purpose but requires hospital admission, is recommended only in endocrine units and is not needed in patients with a florid Cushing's phenotype and other positive tests as detailed in this section: a value <50 nmol/litre effectively excludes Cushing's syndrome.

24-Hour urinary free cortisol: at least three collections are required to avoid missing mild disease. The amount excreted is reduced in renal impairment.

Determining the cause of Cushing's syndrome

After confirming Cushing's syndrome (Figure 2), plasma ACTH is measured. To avoid obtaining falsely low results, samples must be cold-centrifuged immediately after sampling, and 'flash-frozen' (−40°C) before storage for later assay.[1,2,5]

- Plasma ACTH <5 pg/ml (<1.1 pmol/litre) indicates a primary adrenal cause of Cushing's syndrome, and the adrenal glands should be imaged by CT or magnetic resonance imaging (MRI).

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