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Cushing's syndrome

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This article discusses endogenous Cushing's syndrome which is due to prolonged, inappropriate and excessive circulating free cortisol.[1] Exogenous glucocorticoids are a frequent cause so an adequate medication history is essential.

Epidemiology, prognosis and causes

Patients with severe Cushing's syndrome have a fivefold excess mortality. Reported prevalence is low (0.7–2.4/million population) with a mean of onset of 36 years. However, recent data show that 2–5% of obese patients with poorly controlled type 2 diabetes and hypertension have biochemical Cushing's and benefit from treatment for their cortisol excess.[2] This suggests that widespread screening for Cushing's syndrome in such populations may be warranted but it is not yet established. Causes of Cushing's syndrome are listed in Table 1.

Clinical features (Table 2)

Clinical features vary among patients and may fluctuate in a 'cyclical fashion' causing diagnostic difficulty. The signs most reliably distinguishing Cushing's from simple obesity are thin skin, easy bruising, proximal myopathy and, in children, decreased linear growth.[3]

Biochemical evaluation

Biochemical evaluation involves two steps:

- establishing a diagnosis of hypercortisolaemia
- defining the cause.

Biochemical diagnosis of hypercortisolaemia (Fig 1)

Clinical suspicion usually prompts evaluation, but certain patient groups may warrant screening,[1] for example:

- poorly-controlled, hypertensive patients with diabetes
- unexplained osteoporosis.

Hypercortisolaemia is also found in some patients with depression, alcohol dependence, anorexia nervosa and late pregnancy. In contrast to true endogenous Cushing's syndrome, in these situations the biochemistry improves when the underlying condition has resolved.

Table 1. Aetiology of Cushing's syndrome.

Cause	%	Female: Male	Female (%)	Male (%)
ACTH-dependent:				
Cushing's disease (pituitary)	70	3.5:1	90	60–70
Ectopic ACTH syndrome[a]	10	1:1	10	30
Unknown source of ACTH[b]	5	5:1		
ACTH-independent:				
Adrenal adenoma	10	4:1		
Adrenal carcinoma	5	1:1		
Macronodular hyperplasia	<2			
Primary pigmented nodular adrenal disease[c]	<2			
McCune Albright syndrome	<2			

[a]Most common causes: small-cell lung cancer, bronchial carcinoid tumours.
[b]Patients may ultimately prove to have Cushing's disease.
[c]Sporadic or as part of Carney complex (atrial myxoma, cutaneous lentigines, pituitary tumours – germline mutations of the regulatory subunit R1A of PKA *(PRKAR1A)* are present in approximately 45% of patients with Carney complex).

Investigations should be performed when there is no acute concurrent illness, as this may cause false positive results. If in doubt, tests should be repeated or further opinion sought.

Low-dose dexamethasone-suppression tests. Two tests are in common use:

1 The overnight dexamethasone-suppression test in which 1 mg of dexamethasone is administered at 23.00 hours and serum cortisol measured the next day at 08.00–09.00 hours.
2 The 48-hour test in which 0.5 mg dexamethasone is administered every six hours for two days, at 09.00 hours, 15.00 hours, 21.00 hours and 03.00 hours, with measurements of serum cortisol at 09.00 hours at the start and end of the test.

The 48-hour test has greater diagnostic accuracy and, with adequate written instructions, can routinely be performed in outpatients. Following either test, the serum cortisol should be below 50 nmol/l to exclude Cushing's syndrome.[3,4]

Importantly, 3–8% of patients with Cushing's disease (pituitary) show suppression of serum cortisol to below 50 nmol/l on either test (false negative).[5,6] Thus, if clinical suspicion remains high, repeated tests and other investigations are indicated. False positive responses may result from:

- malabsorption of dexamethasone
- drugs that increase hepatic clearance of dexamethasone, including carbamazepine, phenytoin, phenobarbital or rifampicin
- oestrogen therapy or pregnancy which increases cortisol binding globulin (CBG), and thus the total cortisol as measured by most assays. Oral oestrogens need to be stopped for a period of 4–6 weeks so that CBG may return to basal values prior to evaluation.[1]

24-hour urinary free cortisol. The least sensitive of tests for diagnosis of Cushing's is urinary free cortisol (UFC); three 24-hour collections are needed to avoid missing mild or cyclical disease. Values four-fold greater than the upper limit of normal are rare except in Cushing's. Levels of UFC frequently overlap those seen in patients with other causes of hypercortisolaemia. If there is renal impairment or an incomplete collection, the UFC may be falsely low.[1,4]

Midnight plasma cortisol. The normal circadian rhythm of cortisol secretion is lost in patients with Cushing's syndrome. A single sleeping midnight plasma cortisol below 50 nmol/l effectively excludes Cushing's syndrome.[7] This may be particularly helpful where there has been incomplete suppression on dexamethasone testing, but it is difficult to perform on a general inpatient ward and is usually done in dedicated endocrine units. An awake midnight plasma cortisol of over 207 nmol/l is in keeping with Cushing's but may miss 7% of mild disease.[8]

Late-night salivary cortisol. Salivary cortisol reflects free circulating cortisol; it is both easy to collect and stable at room temperature, making it a highly suitable screening tool for outpatient assessment.[9,10]

Currently, there is no widespread access to salivary cortisol assays in the UK. The values of salivary cortisol are an order of magnitude lower than serum cortisol, so it is essential that the performance of any assay is known and the appropriate cut-off point utilised.

Table 2. Clinical features of Cushing's syndrome (most discriminating features in bold).

Feature	%
Obesity or weight gain	95*
Facial plethora	90
Rounded face	90
Decreased libido	90
Thin skin	85
Decreased linear growth in children	70–80
Menstrual irregularity	80
Hypertension	75
Hirsutism	75
Depression/emotional lability**	70
Easy bruising	65
Glucose intolerance	60
Proximal myopathy	60
Osteopenia or fracture	50
Nephrolithiasis	50

*100% in children.
** May persist for years after biochemical remission. Ectopic ACTH syndrome due to small-cell lung cancer may have a rapid onset and severe biochemical features, but the classic Cushing's phenotype may not have time to develop. In contrast, the clinical phenotype of carcinoid tumours may be very similar to that of Cushing's disease.

Differential diagnosis: determining the cause of Cushing's syndrome (Fig 2)

The first step in the differential diagnosis of Cushing's is to measure plasma ACTH. Plasma should be separated rapidly and stored at –40°C to avoid degradation and a falsely low result. Levels consistently below 5 pg/ml indicate ACTH-independent

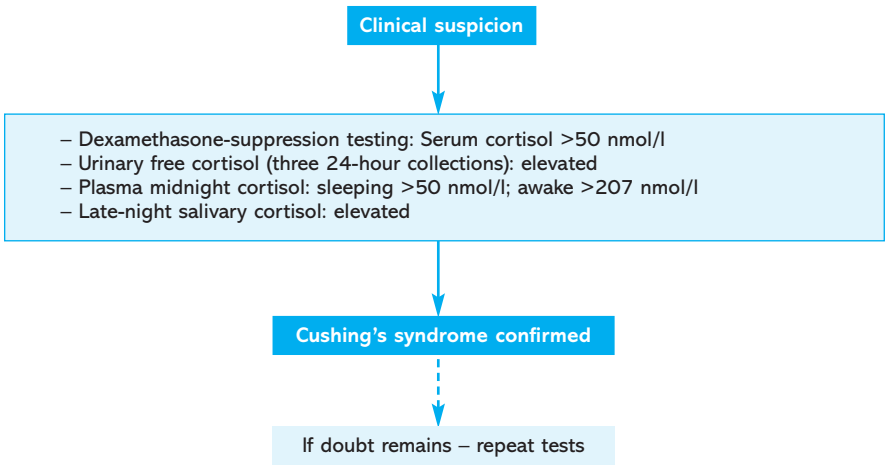

Fig 1. Diagnosis of Cushing's syndrome.

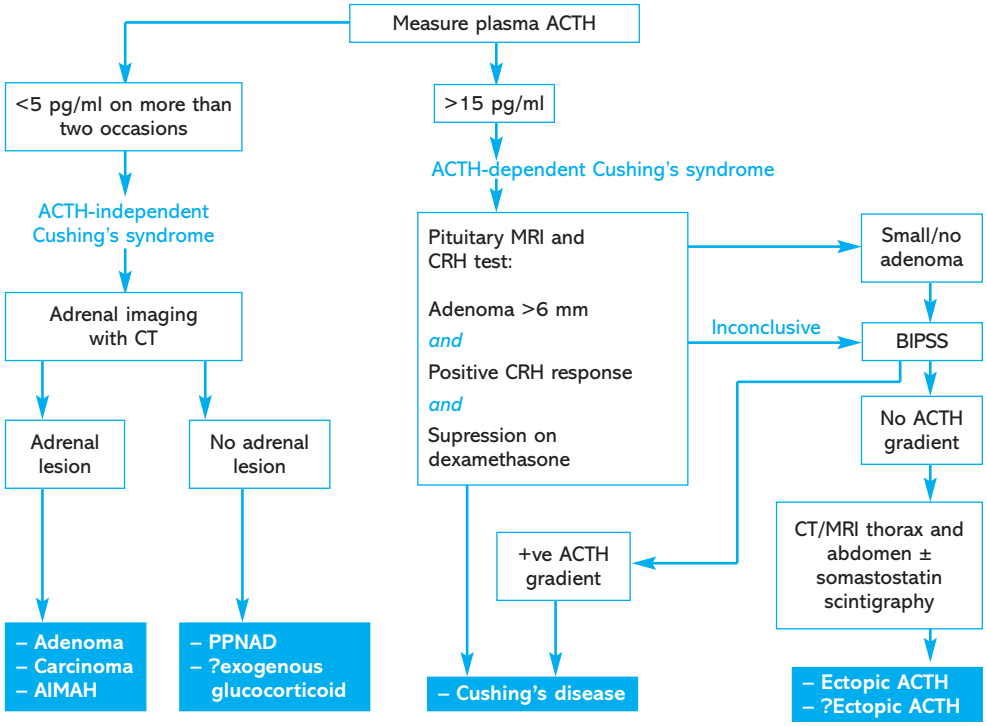

Fig 2. Differential diagnosis of Cushing's syndrome. AIMAH = ACTH-independent macronodular hyperplasia; BIPSS = bilateral inferior petrosal sinus sampling; CRH = corticotropin-releasing hormone; CT = computed tomography; MRI = magnetic resonance imaging; PPNAD = primary pigmented nodular adrenal disease; SCLC = small cell lung cancer.

Cushing's syndrome and those persistently above 15 pg/ml almost always reflect ACTH-dependent pathologies and require investigation (as detailed below). Values between these two need cautious interpretation as occasionally patients with Cushing's disease (pituitary) and adrenal pathologies may have intermediate values.[1,3]

ACTH-independent Cushing's syndrome

ACTH-independent Cushing's syndrome (Table 1) is caused by an adrenal adenoma, carcinoma or ACTH-independent macronodular hyperplasia (AIMAH). The anatomical cause is invariably visible on imaging with computed tomography (CT). The adrenal glands may appear normal in primary pigmented nodular adrenal disease (PPNAD).

ACTH-dependent Cushing's syndrome

Magnetic resonance imaging (MRI) of the pituitary is normal in 40% of patients with Cushing's disease (pituitary source of excess ACTH) and 10% of the general population have pituitary incidentalomas, so differentiation between pituitary and non-pituitary sources relies on biochemical evidence.[1,3] Hypokalaemia is more common in the ectopic ACTH syndrome but is also present in 10% of Cushing's disease. Approximately 90% of ACTH-dependent Cushing's syndrome cases are Cushing's disease (pituitary). The time-honoured high-dose dexamethasone-suppression test has a sensitivity for the diagnosis of Cushing's disease that is less than the chance of having this condition and thus does not add useful information and is no longer recommended

Key Points

- **Cushing's disease (pituitary) is the most common form of endogenous Cushing's syndrome**
- **The most discriminating clinical features for Cushing's syndrome in adults are the presence of thin skin, easy bruising and proximal myopathy**
- **Diagnosis of hypercortisolaemia (Cushing's syndrome) *must* be established before any attempt at differential diagnosis**
- **The best tests to screen for Cushing's are low-dose dexamethasone-suppression tests, up to three 24-hour urinary free cortisol samples and late-night salivary cortisol, if available (midnight serum cortisol is best done in dedicated inpatient investigation units)**
- **Once Cushing's syndrome is established, the next step is measurement of plasma ACTH**
- **Differential diagnosis and management of Cushing's syndrome are best undertaken in major referral centres**
- **Adrenal surgery should be performed by endocrine surgeons expert in laparoscopic techniques, and pituitary surgery in centres with major experience of pituitary surgery**

KEY WORDS: ACTH, adrenal, cortisol, Cushing's syndrome, dexamethasone, pituitary

where bilateral inferior petrosal sinus sampling (BIPSS) is available (see below).[1] Data from the 48-hour low-dose dexamethasone-suppression test can be useful: a 30% fall in serum cortisol is suggestive of Cushing's disease,[6] as is a rise of over 15% in mean plasma cortisol 15 min and 30 min after intravenous administration of 100 μg of corticotropin-releasing hormone (CRH).[11]

Bilateral inferior petrosal sinus sampling

BIPSS is a highly skilled and invasive technique, requiring placement of catheters in both inferior petrosal sinuses, and must only be performed in major referral centres. A basal central to peripheral ratio of above 2:1 or a CRH-stimulated ratio of over 3:1 is consistent with Cushing's disease, with a sensitivity and a specificity of 94%.[12]

Imaging

Over 85% of cases of Cushing's disease are due to a pituitary microadenoma (<1 cm), and MRI is the imaging modality of choice. Imaging with thin-cut multislice CT or MRI of thorax and abdomen has the highest detection rate for the ectopic ACTH syndrome.[1,3] Neuroendocrine tumours may be shown on somatostatin receptor scintigraphy, but this has only rarely disclosed truly 'occult' tumours not visible on CT. Despite extensive investigation, the source of ACTH may remain 'occult' in 5–15% of patients; these patients require continued follow-up.[13,14]

Surgery

Transsphenoidal surgery

Transsphenoidal selective microadenomectomy by an experienced surgeon is the treatment of choice for the vast majority of patients with Cushing's disease, However, it provides long-lasting remission in only 50–60% of cases, emphasising the need for other effective treatments to lower ACTH in Cushing's disease.[1]

Adrenal surgery

Laparoscopic unilateral adrenalectomy by an experienced surgeon is the treatment of choice for patients with an isolated adrenal adenoma. There is a good prognosis following removal of adrenocortical cortisol-secreting adenoma. In contrast, the prognosis is almost uniformly very poor in patients with adrenocortical carcinomas.

For any cause of ACTH-dependent Cushing's syndrome, bilateral adrenalectomy may be required to achieve adequate control of the circulating cortisol levels. A major concern following bilateral adrenalectomy in patients with refractory Cushing's disease is the development of Nelson's syndrome – a potentially locally aggressive pituitary tumour that secretes high levels of ACTH resulting in pigmentation. This can be monitored and the tumour itself treated with further surgery and radiotherapy if needed.[15]

Ectopic ACTH

Complete excision of an ACTH-secreting tumour usually results in long-lasting remission, unless it is metastatic.

Medical therapy to reduce cortisol

In preparation for surgery or following unsuccessful surgery medical therapy may be used to lower cortisol. It is rarely a good long-term solution and is mainly used as adjunctive treatment to other modalities such as surgery and pituitary radiotherapy. Metyrapone (500–1,000 mg tds/qds, dose increments every 72 hours) and ketoconazole (200–400 mg tds, dose increments at 2–3 weekly intervals) inhibit cortisol synthesis, aiming for a mean plasma cortisol level of 150–300 mmol/l or normalisation of elevated UFC. Metyrapone, but not ketoconazole, causes an increase in steroid androgenic precursors and hirsutism is a major adverse effect in women when using metyrapone. In the UK o,p'DDD (Mitotane), an adrenolytic agent, is usually reserved for the treatment of adrenocortical carcinoma. Recent studies on the use of rosiglitazone and cabergoline to lower plasma ACTH and hence cortisol in Cushing's disease have had disappointing results.[1]

Pituitary radiotherapy

Following transsphenoidal surgery, persisting hypercortisolaemia may be treated with pituitary radiotherapy. Progressive anterior pituitary failure is the major side effect; in particular, growth hormone deficiency is virtually uniform 10 years after treatment and gonadotrophin deficiency is present in about 15%.

Conclusions

Diagnosis and management of Cushing's syndrome still present considerable challenges and patients warrant referral to major centres. Cushing's syndrome may be present in a significant minority of poorly controlled type 2 diabetics, with considerable implications for screening of this at-risk population. Salivary cortisol is a promising screening tool and may be particularly suited for this purpose. The outcome of treatment for Cushing's disease remains disappointing in many patients. Further developments are needed in this area.

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Abnormal thyroid stimulating hormone levels: when and who to treat

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Thyroid stimulating hormone (thyrotropin, TSH) measurement is the most widely used test to determine whether a patient has thyroid dysfunction. There is a negative feedback loop between the thyroid and pituitary so TSH levels represent a tissue response to ambient thyroid hormone levels. When pituitary function is normal, the inverse relationship between serum TSH and free thyroxine (FT4) levels is log/linear: a small increase in FT4 will produce a large decrease in TSH and vice versa. Thus, an abnormal TSH level is a sensitive, but not specific, marker of thyroid dysfunction.

Measurement of thyroid stimulating hormone

Improvements in methodology have increased the sensitivity of TSH measurement, with third-generation assays routinely able to detect levels as low as 0.02 mU/l. Dynamic testing of TSH responses (eg to thyrotropin-releasing hormone) are now redundant.

Abnormal thyroid stimulating hormone

When is the thyroid stimulating hormone abnormal?

Physicians frequently talk about 'normal range' when discussing laboratory values, but biochemists use 'reference range'. The latter term comprises 95% of measurements made on healthy volunteers. 'Reference range' is not only semantically correct but also emphasises that in any test some healthy individuals will have values outside the range. TSH levels within a healthy population are not normally distributed but have a long tail of values towards the upper limit.

Some individuals in the upper half of the reference range may develop hypothyroidism decades later,[1] leading to recent suggestions that the TSH reference range is too wide as it includes individuals who may already have mild thyroid autoimmune damage.[2] However, the reference range of TSH is unchanged when individuals in populations with a normal iodine intake are rigorously screened to exclude any evidence of thyroid autoimmunity.[3] Therefore, current reference ranges for TSH remain around 0.4–4.5 mU/l, with some variation between laboratories depending on the exact assay method used.[4]

Table 1. Causes of raised thyroid stimulating hormone (TSH).

Cause of raised TSH	Free thyroid hormone level
Primary hypothyroidism:	
Overt	↓
Subclinical	N
Poor adherence to levothyroxine replacement	↑, N or ↓
Assay interference (heterophilic antibodies)	N
Non-thyroidal illness (recovery phase)	N or ↓
Some cases of TSH-receptor resistance	N or ↓
Secondary hyperthyroidism:	
Some cases of TSH-secreting adenoma*	↑
Some cases of thyroid hormone resistance**	↑

* TSH is immunoreactive but bioinactive.
** Patients are euthyroid; elevated free thyroid hormone levels compensate for relative resistance.