PEER REVIEWED

Cushing's syndrome versus simple obesity

How can a needle be found in the haystack?

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Clinical recognition of Cushing's syndrome should generally follow from the observation of a constellation of compatible clinical features that progress over time. Screening for Cushing's syndrome in patients with individual features of the metabolic syndrome, such as obesity, hypertension and hyperglycaemia, is not recommended. Early diagnosis reduces unnecessary suffering and the ultimate lifetime sequelae of Cushing's syndrome. Confirmation involves the demonstration of biochemical hypercortisolism, and the extent of diagnostic testing needs to be based on the degree of clinical suspicion.

Key points

- **A diagnosis of Cushing's syndrome depends on the recognition of a constellation of compatible clinical features that progress over time.**
- **The tests for confirmation of hypercortisolism are the 24-hour urine free cortisol test, 1 mg overnight dexamethasone suppression test and the late night salivary cortisol test. All three tests may have false-negative and false-positive results, and results close to laboratory normal cut-offs should be regarded as nondefinitive.**
- **The extent of testing for hypercortisolism depends on the degree of clinical suspicion and the results of initial testing.**

Cushing's syndrome is a clinical syndrome caused by excessive tissue exposure to glucocorticoids. It may occur as a result of hypercortisolism in which there are elevated circulating levels of the endogenous glucocorticoid cortisol. This is known as endogenous Cushing's syndrome and it is rare, with an incidence of three to 10 cases per million persons per year. Endogenous Cushing's syndrome may be caused by a pituitary tumour or extrapituitary (ectopic) adrenocorticotrophic hormone (ACTH)-secreting tumour or by functional benign or malignant tumours of one or both adrenal cortices. By contrast, exogenous Cushing's syndrome is caused by exposure to exogenous glucocorticoids, such as prednisolone, and is the more common form of Cushing's syndrome, as the use of synthetic glucocorticoids for inflammatory diseases has a prevalence of 1 to 3%.

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1. Causes of pseudo-Cushing's syndrome[1]

- Chronic alcoholism
- Psychological stress, melancholic depression
- Physical stress – severe bacterial infection, trauma, pain, hypovolaemia
- Malnutrition, anorexia nervosa
- Intense long-term exercise

Hypercortisolism is not always due to Cushing's syndrome; it may be due to physiological hypercortisolism or pseudo-Cushing's syndrome. In these cases, hypercortisolism may be caused by activation of the stress response system due to conditions such as chronic alcoholism, melancholic depression and malnutrition (see Box 1). Physiological hypercortisolism is also evident in pregnancy.

Hypothalamic–pituitary–adrenal axis and cortisol production

Cortisol is a product of the adrenal cortex zona fasciculata and is regulated by pituitary ACTH, the secretion of which is controlled by the hypothalamic secretagogues corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP). This system is known as the hypothalamic–pituitary–adrenal (HPA) axis. The three regulatory influences of this system are:

- stress, defined as any threat to homeostasis, such as inflammation or trauma
- the circadian rhythm (Figure 1)
- negative feedback, in which cortisol inhibits HPA activity at the level of the pituitary and hypothalamus, and influences higher centres such as the hippocampus.

The inflammatory cytokines, particularly interleukin-6, are key drivers of the stress response and are produced in excess in obesity.

Cortisol secretion is regulated in synchrony with the sympathetic nervous system, comprising sympathoneural (noradrenaline) and sympathoadrenal (adrenaline 80%, noradrenaline 20%) outputs. Connections between the HPA axis and these catecholaminergic systems exist at the level of the midbrain/pons and at the adrenal itself, where cortisol promotes the conversion of noradrenaline to adrenaline. The co-ordinated response of the HPA axis and sympathetic nervous system to stressors is known as the stress system (Figure 2).

In blood, cortisol is transported 80% bound to corticosteroid-binding globulin (CBG). Measurements of cortisol in blood are considered to represent total cortisol (CBG bound plus albumin bound and free) whereas measurements in urine or saliva represent the free fraction, which is generally only 5% of circulating cortisol.

In Cushing's syndrome, normal HPA axis regulation is disturbed. Diagnosis of Cushing's syndrome depends on the demonstration of these disturbances, namely increased cortisol secretion (24-hour urine free cortisol test), blunted negative feedback (dexamethasone suppression test), reduced circadian rhythmicity of cortisol (late night plasma and salivary cortisol tests) and exaggerated responses to the hypothalamic secretagogues CRH and AVP.

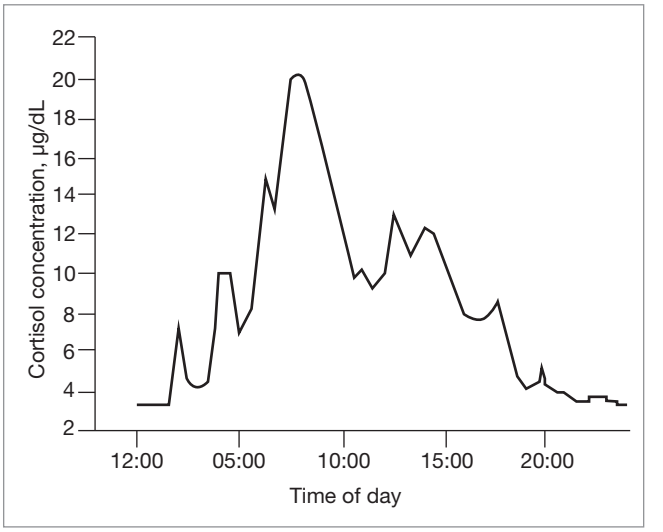


Figure 1. Circadian rhythm of the hypothalamic–pituitary–adrenal (HPA) axis. Cortisol levels rise at times of increased HPA activity and after meals.
(Note: nmol/L = µg/dL x 27.59)

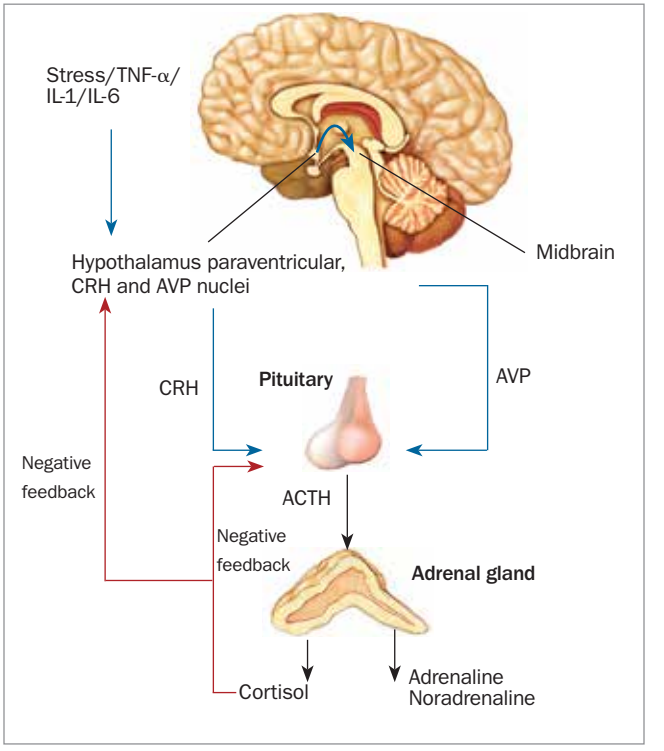


Figure 2. Hypothalamic–pituitary–adrenal axis and the stress system.
Abbreviations: ACTH = adrenocorticotrophic hormone; AVP = arginine vasopressin; CRH = corticotrophin- releasing hormone; IL = interleukin; TNF = tumor necrosis factor.

2. Features of Cushing's syndrome[1]

More discriminatory features

Symptoms, medical history (especially at a young age)

- Hypertension
- Diabetes mellitus
- Osteoporosis with vertebral fractures

Signs

- Facial plethora
- Proximal myopathy
- Cutaneous striae >1 cm wide
- Bruising
- Weight gain (with reduced height percentile in children)

Less discriminatory features

Symptoms, medical history

- Fatigue, proximal weakness
- Weight gain, altered fat distribution
- Striae
- Depression, mood and appetite change
- Impairment of concentration and memory
- Back pain, without stress fractures
- Oligomenorrhoea, polycystic ovary syndrome
- Recurrent infection

Signs

- Central obesity
- Buffalo hump (interscapular fat pad), supraclavicular fullness
- Facial fullness
- Acne and hirsutism
- Skin thinning
- Poor wound healing
- Peripheral oedema

When to suspect Cushing's syndrome

The clinical features of Cushing's syndrome are due to the effects of excess cortisol on various tissues. The severity of clinical features is proportionate to the degree and duration of hypercortisolism. The major features of Cushing's syndrome are listed in Box 2, categorised according to those features that are more discriminatory (i.e. more likely to represent Cushing's syndrome) and those that are less discriminatory. Clinical signs of Cushing's syndrome are shown in Figures 3a to e.

The clinical diagnosis of Cushing's syndrome requires the recognition of an array of clinical features, appearing over a similar period and exhibiting progression over time. These clinical features may be categorised into those of body composition (gain in fat, skin thinning, muscle wasting and bone loss), metabolic features (hyperglycaemia and hypertension) and neuropsychological features (disturbed mood, attention span and cognition).

Early stages

In the early stages, Cushing's syndrome may resemble the metabolic syndrome, with abdominal obesity, hypertension, dyslipidaemia and hyperglycaemia as the presenting features. As 20 to 30% of adults have metabolic syndrome, these nonspecific features may not be sufficient to prompt further investigation. Although a diagnosis typically occurs two years after the onset of symptoms, the diagnosis can be delayed as long as 20 years.[2,3] Rapid weight gain may lead to an early diagnosis of Cushing's syndrome. Typically, Cushing's syndrome is associated with central or truncal obesity (common in both men and women), rather than excess adiposity in regions such as the buttocks and thighs, which is more often seen in women, and is sometimes referred to as gynoid obesity. Morbid obesity is rarely associated with Cushing's syndrome unless the patient had pre-existing obesity.

Several studies have shown that screening for Cushing's syndrome in obese people with diabetes has a low yield. One study screened 813 patients with obesity and type 2 diabetes, of whom six were confirmed to have Cushing's syndrome (less than 1%).[5] However, another study investigated 150 obese patients for Cushing's syndrome and found 14 confirmed cases.[6] After a review of the currently available data, a study concluded that routine screening for Cushing's syndrome in obese patients with diabetes had more drawbacks, such as cost and false-positive results, than could be justified on the basis of confirmed diagnoses of Cushing's syndrome.[4]

Hypertension in people with Cushing's syndrome is relatively resistant to antihypertensive drugs and may be associated with hypokalaemia, particularly when coupled with severe hypercortisolism (i.e. urine free cortisol levels in excess of 10-fold normal).[7]

Patients with Cushing's syndrome usually develop neuropsychological symptoms, including a loss of equanimity, a tendency to anger over small frustrations, and reduced attention span and concentration. People with more advanced Cushing's syndrome may have melancholic depression and cognitive impairment.[8-10] Patients with severe Cushing's syndrome can develop florid psychotic symptoms.[11] Some patients, particularly those with severe, rapid onset hypercortisolism, may present with neurocognitive manifestations, such as is often seen in people with Cushing's syndrome due to an ectopic ACTH-secreting tumour.[7]

Cushing's syndrome often disturbs the hypothalamic–pituitary–gonadal axis. Oligomenorrhoea is common in reproductive age women. This and other features, such as central obesity and hirsutism due to excess adrenal androgens, can mimic polycystic ovary syndrome (PCOS). A distinguishing feature is that in people with PCOS, gonadotrophin (follicle-stimulating hormone, luteinising hormone) levels are not suppressed, whereas they frequently are in people with Cushing's syndrome.

Later stages

Cushing's syndrome progresses beyond the initial stages of features of the metabolic syndrome and mild neuropsychological disturbance to a catabolic stage. Catabolic features relate to protein metabolism and include thinning of skin, striae and ecchymoses, muscle weakness and wasting, and bone loss leading to osteoporosis with fractures, with the extent depending on the severity and duration of hypercortisolism. Severe prolonged Cushing's syndrome can cause immunosuppression and predisposes to opportunistic infections as well as severe psychiatric manifestations such as psychosis.

In people with Cushing's syndrome, in contrast to obesity, stretch marks on the abdomen, breast or upper arms may be greater than 1 cm in width, with a purplish or violaceous appearance. Easy bruising and osteoporosis are not features of simple obesity. Similarly, proximal myopathy is not a feature of obesity and its presence strongly favours Cushing's syndrome over obesity. Proximal lower limb strength can be conveniently assessed by asking the patient to stand from a squatting position (while you hold their hands to avoid a fall but asking them not to use your arms as a lever). Similarly, upper limb weakness can be tested with pressure over the outstretched flexed elbows. Osteoporosis caused by Cushing's syndrome may cause fractures of vertebrae and peripheral bones, such as small bones of the feet. Importantly, however, early Cushing's syndrome is often associated with osteopenia or even normal bone density on dual-energy x-ray absorptiometry despite fractures, as bone fragility increases more markedly than predicted by the small decline in bone mineral density.

Clinical features and causes of Cushing's syndrome

Pituitary Cushing's syndrome (Cushing's disease), which is caused by an ACTH-secreting adenoma of the pituitary, has a typical progression of Cushing's features as described above. It accounts for at least 70% of endogenous cases of Cushing's syndrome. Adrenal Cushing's syndrome due to unilateral or bilateral, usually benign, adrenal cortical tumours (20% of endogenous cases) often presents similarly.

Ectopic Cushing's syndrome due to an ACTH-secreting neuroendocrine tumour outside the pituitary (e.g. bronchial carcinoid tumour, pancreatic neuroendocrine tumour, medullary thyroid carcinoma) may present with slow or rapid onset of Cushing's features. Ectopic Cushing's syndrome caused by large, highly malignant neuroendocrine tumours, such as small cell carcinoma of the lung, often causes an abrupt onset of severe hypercortisolism, leading to hypertension, hypokalaemia, muscle dysfunction and neuropsychiatric features, often without weight gain or the metabolic features seen in pituitary Cushing's syndrome that generally have a gradual onset and course.

Diagnostic approach to Cushing's syndrome

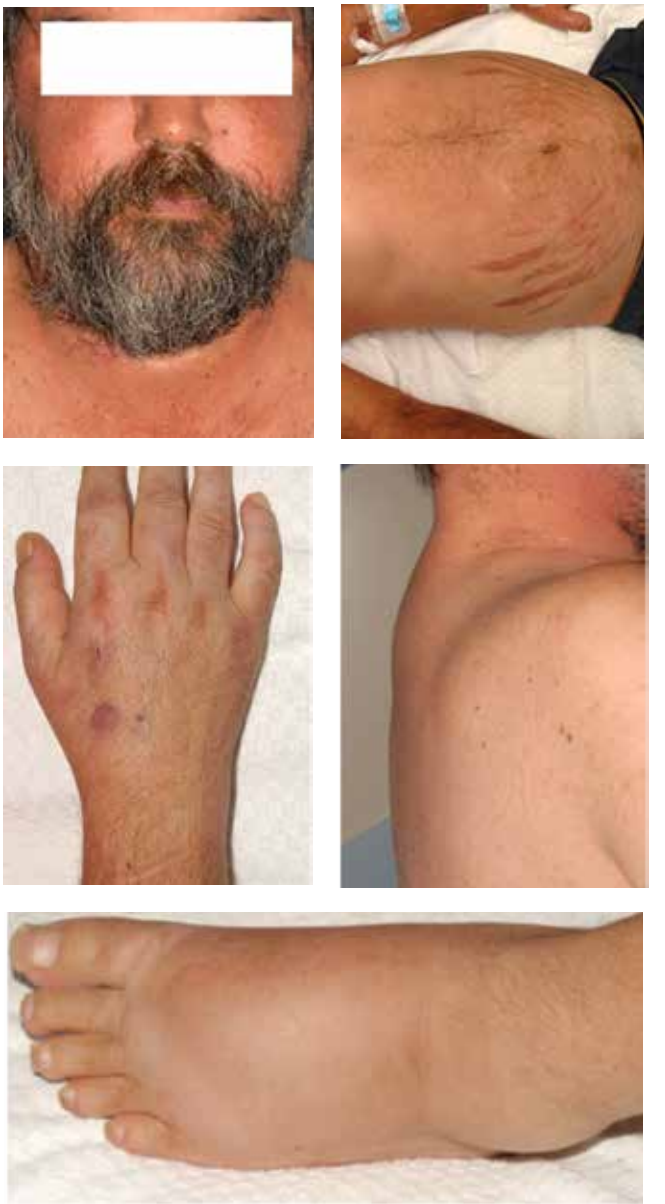
The first stage of diagnosis after clinical suspicion of Cushing's syndrome is the demonstration of hypercortisolism. The three first-line screening tests are:

- 24-hour urine free cortisol test
- overnight 1 mg dexamethasone suppression test
- late night salivary cortisol test.

Approximately 10 to 20% of individuals may have false-positive or false-negative results of individual screening tests.

24-hour urine free cortisol test

Urine free cortisol level of less than threefold normal in 24 hours (mild hypercortisolism) without prominent clinical features of Cushing's syndrome could be due to pseudo-Cushing's syndrome caused by depression, excess alcohol intake, physical illness or active stressors (see Box 1). Urine free cortisol levels more than threefold normal in 24 hours are likely to represent true Cushing's syndrome, although some patients with Cushing's syndrome may have urine free cortisol levels in the high normal range.



Figures 3a to e. Signs of Cushing's syndrome. a (top left). Facial fullness. b (top right). Central obesity with pigmented striae. c (centre left). Easy bruising. d (centre right). Buffalo hump. e (above). Peripheral oedema.

A positive result, particularly if it is close to the diagnostic cut-off, in a patient with a lower degree of clinical suspicion should prompt repeat or alternative testing. The 24-hour urine free cortisol test measures levels of cortisol plus other metabolites and represents cortisol secretion over a 24-hour period. It is essential to measure the concomitant creatinine excretion to establish that the urine collection was complete. Creatinine excretion varies in accordance with body

size and muscle mass and should not vary by more than 10 to 20% between collections. High urine outputs (greater than 4 litres) may elevate the urine free cortisol level and the test is invalid in people with renal impairment (creatinine clearance rate <60 mL/min). Some individuals with pseudo-Cushing's syndrome may have mild hypercortisolaemia in association with milder Cushing's syndrome (gain in fat, skin thinning, muscle wasting and bone loss, and features of the metabolic syndrome); this will not respond to pituitary surgery and generally remits over time.

Dexamethasone suppression test

The dexamethasone suppression test relies on impaired glucocorticoid negative feedback on the HPA axis, present to variable degrees in all forms of Cushing's syndrome. In the overnight dexamethasone suppression test, 1 mg dexamethasone is given orally at 11 pm, and plasma cortisol is measured at 9 am. The current recommended normal range is less than 50 nmol/L; this cut-off reduces false-negative results but gives a substantial false-positive rate in patients in whom the possibility of Cushing's syndrome is being considered. Drugs that increase the metabolism of dexamethasone, such as phenytoin, carbamazepine and drugs that increase CBG and hence cortisol levels such as the oral contraceptive pill, can elevate the post-dexamethasone cortisol level and produce a false-positive result.

Late night salivary cortisol test

Measurement of late night salivary cortisol levels can demonstrate the loss of the normal nocturnal cortisol nadir in patients with Cushing's syndrome and has evolved as a more convenient option to the midnight sleeping plasma cortisol test.[12] Collection of saliva allows measurement of free cortisol separate from CBG- and albumin-bound cortisol. Salivary cortisol concentrations are only about 5% of plasma concentrations, and therefore a very sensitive assay for measurement is required Saliva samples can be collected at home using a salivette device. Specific diagnostic cut-offs need to be established for each assay.

Which test to use?

The sensitivity and specificity of the three main tests for hypercortisolism described above are similar at about 80 to 90%.[13]

Clinical suspicion of Cushing's syndrome should prompt testing for hypercortisolism. In most cases, the 24-hour urine free cortisol test is the preferred initial diagnostic test for Cushing's syndrome. Levels below the midpoint of the normal range usually exclude Cushing's syndrome. A significant proportion of patients worldwide diagnosed with Cushing's syndrome (perhaps 15%) have 24-hour urine free cortisol levels in the upper normal range. However, as some people without Cushing's syndrome have mild elevations of 24-hour urine free cortisol, it is not possible to establish a fully reliable upper limit of normal for

this test. 24-hour urine collections are, however, inconvenient and cumbersome. The 1 mg overnight dexamethasone suppression test is a useful screening test, but lack of suppression is quite common in patients who do not have Cushing's syndrome. However, suppression of plasma cortisol to less than 50 nmol/L makes Cushing's syndrome very unlikely. The late night salivary cortisol is the third option for testing. It is convenient but often limited by an insufficient saliva sample and falsely elevated results caused by several factors and a tendency for higher results in older patients with comorbidities.[14]

There is no ideal screening test for Cushing's syndrome. Repeat tests can be informative, particularly as some patients exhibit cyclic or intermittent Cushing's syndrome, in which a single test may be misleadingly normal.

Generally, when clinical suspicion is high, all three tests should be performed and an endocrine opinion should be sought. Positive results should be followed up with measurement of plasma ACTH levels, which helps identify patients with adrenal Cushing's syndrome and the occasional patient with surreptitious use of exogenous glucocorticoids.

Random serum cortisol measurements are of little value in diagnosing Cushing's syndrome because the levels can vary throughout the day.

The distinction between Cushing's syndrome and pseudo-Cushing's syndrome is difficult and requires specialist advice, although some tests such as the dexamethasone-suppressed CRH test have been developed to distinguish these conditions with moderately high accuracy.[15] This test exploits the concept that in pseudo-Cushing's syndrome, higher brain centres stimulate CRH release, leading to activation of the HPA axis.[15]

Details on differential diagnosis and treatment of Cushing's syndrome can be found elsewhere.[16]

Conclusion

Indiscriminate screening for Cushing's syndrome in patients with features common to the metabolic syndrome, such as central obesity, hypertension or hyperglycaemia, is not recommended. However, clinicians should be alert to more discriminatory features that may represent Cushing's syndrome, such as facial plethora, rapid weight gain without explanation, development of acne, hirsutism and oligomenorrhoea in women of reproductive age, a tendency to agitation, anger and depression, poor sleep, unexplained bruising and skin thinning with easy injury, lumbar back pain and distal lower limb fractures. Diagnosis at this stage will considerably benefit the patient by reducing the duration of unnecessary suffering, as treatment, generally surgical, has a high success rate. Recognition of late features, such as metabolic disturbance incorporating hypertension (sometimes with hypokalaemia) or diabetes mellitus and ultimate severe neuropsychiatric disturbance (depression and/or psychosis), osteoporosis with fractures and opportunistic infections, may avoid life-threatening sequelae.

Awareness of the diverse clinical features of Cushing's syndrome and the natural progression of features allows for earlier diagnosis without a need for widespread screening. Suspicion of Cushing's syndrome needs to be based on a constellation of compatible features exhibiting progression over time. The extent of diagnostic/rule-out testing for Cushing's syndrome needs to be based on the degree of suspicion. It is recommended that patients with proven hypercortisolism or those with suggestive clinical features and borderline screening results be referred to an endocrinologist because the diagnosis of mild Cushing's syndrome versus non-Cushing's hypercortisolism requires specific experience. Even with this experience, there is often uncertainty and careful follow up and collaboration between the GP and endocrinologist are needed. **ET**

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