Cushing’s disease

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Cushing’s syndrome refers to the clinical manifestations induced by chronic exposure to excess glucocorticoids. There are three pathological conditions that can result in the chronic overproduction of endogenous cortisol in man: the most frequent is Cushing’s disease where adrenocorticotropic hormone (ACTH) is overproduced by a pituitary corticotroph adenoma, rarely ACTH can be produced in an ‘ectopic’ manner by a non-pituitary tumour, finally cortisol can be directly over-secreted by one or (rarely) the two adrenals that have become tumourous, either benign or malignant.

The positive diagnosis of Cushing’s syndrome requires that chronic hypercortisolism is unequivocally demonstrated biologically, using 24-h urinary cortisol, late-evening plasma or salivary cortisol, midnight 1-mg or the classic 48-h-low-dose dexamethasone suppression test, etc., all with essentially the same diagnosis potencies.

The search for the responsible tumour then relies on the assessment of the corticotroph function, and imaging: suppressed ACTH plasma levels indicate an ‘adrenal’ Cushing, and the responsible unilateral adrenocortical tumour is always visible at computed tomography (CT) scan, whereas its benign or malignant nature may be difficult to diagnose before surgery. Imaging can suspect bilateral ‘adrenal’ Cushing, when the two adrenals are small, as in the primary pigmented nodular adrenal dysplasia associated with Carney complex, or enlarged, as in the ACTH-independent macro-nodular adrenocortical hyperplasia. Measurable or increased ACTH plasma levels indicate either Cushing’s disease or the ectopic ACTH syndrome. When the dynamics of the corticotroph function (high-dose dexamethasone suppression test, the CRH test) are equivocal, and/or the imaging is non-contributive, it may be difficult to
Definition and epidemiology

Cushing’s syndrome refers to the manifestations induced by chronic exposition to glucocorticoid excess and may result from various causes. It most commonly arises from iatrogenic causes, when glucocorticoids are given to treat inflammatory diseases.

In contrast, spontaneous Cushing’s syndrome is rare. It results from various causes that all have in common a chronic over-secretion of cortisol by the adrenals (Table 1).\(^1\)\(^-\)\(^3\)

Cushing’s disease is the most common cause of spontaneous Cushing’s syndrome, occurring in 60–70% of Cushing’s patients. It results from the hypersecretion of adrenocorticotropic hormone (ACTH) by a pituitary corticotroph adenoma.

Ectopic ACTH syndrome is responsible for 5–10% of the cases of spontaneous Cushing’s syndrome; it is caused by a variety of ACTH-secreting non-pituitary tumours.

About 20–30% of spontaneous Cushing’s syndromes are independent of ACTH and are caused by primary adrenocortical tumours.

Spontaneous Cushing’s syndrome is rare; the estimated incidence is about 0.7–2.4 per million per year.\(^4\)\(^-\)\(^6\) There is a high female-to-male ratio (about 3–5:1), except in ectopic ACTH syndrome.\(^1\)\(^,\)\(^2\)

Aetiopathology

The proposition that the pituitary was responsible for the clinical features of Cushing’s disease was convincingly expressed for the first time by Harvey Cushing in his classic monograph of 1932 (The basophil adenomas of the pituitary body and their clinical manifestations. Cushing H 1932. Bull Johns Hopkins Hosp 50;137–95).

A pituitary corticotroph adenoma is present – and can be detected at surgery – in the vast majority of patients with Cushing’s disease. Most are microadenomas, arbitrarily defined as being less than
10 mm with a mean of approximately 6 mm. The classic basophilic adenoma is made of a more-or-less homogeneous collection of corticotroph cells that are ultimately specifically recognised by immunohistochemistry with antibodies directed against the ACTH molecule, or other proopiomelanocortin (POMC, the polypeptide precursor to ACTH)-derived epitopes.

In Cushing’s disease, pituitary ACTH over-secretion induces bilateral adrenocortical hyperplasia and an excess production of cortisol, adrenal androgens and 11-deoxycorticosterone.

The hallmark of ACTH over-secretion in Cushing’s disease is its partial resistance to the normal suppressive effect of glucocorticoids. Because ACTH secretion by the pituitary tumour is not normally restrained, ACTH is over-produced and results in subsequent chronic hypercortisolism. Since peripheral tissues have retained their normal sensitivity to the action of cortisol, they appropriately develop the features of Cushing’s disease.

In contrast with some other endocrine functions in human, chronic adrenocortical stimulation by ACTH does not induce a desensitisation state. Indeed, the opposite occurs: the adrenocortical response is amplified, and it is not unusual to observe a very high secretion of cortisol in face of ‘normal’ (but constant and inappropriate) ACTH plasma levels.

In response to ACTH, various growth factors are locally produced: insulin-like growth factor 1 (IGF1), basic fibroblast growth factor (bFGF) and IGF2 participate in stimulating corticosteroid production, the growth of the adrenals and the adrenal vascular system as well.

The mechanisms of adrenal androgen secretion are grossly parallel with that of cortisol. Thus, dehydroepiandrosterone (DHEA), DHEA sulphate and androstenedione are elevated in ACTH-dependent Cushing’s disease. Their peripheral transformation to testosterone and dihydrotestosterone may lead to a state of androgen excess in females.

ACTH and the lipotropins (β- and γ- LPHs), both derive from the enzymatic processing of their common polypeptide precursor, POMC, and are secreted in equivalent molar quantities by the corticotroph cells. The three peptides share a common melanocyte-stimulating activity through the melanocortin receptor type 2 (MC-R2), and they may cause skin hyper-pigmentation when the corticotroph adenoma is hyperactive: this occurs mainly in the Nelson’s syndrome (see further).

ACTH over-secretion most commonly induces adrenocortical bilateral simple diffuse hyperplasia. The two glands are symmetrically (and generally moderately) enlarged, weighing between 5 and 12 g each at operation. The glands are yellow or brown, and the cortex appears regularly widened on section. A multinodular hyperplasia is present whenever one or several macroscopic yellow nodules are present. Such glands, in general, have a greater weight than in simple diffuse hyperplasia. The size of the nodules displays an extremely wide range of variation, from a few millimetres to several centimetres. Although as a rule they occur in both glands, marked asymmetry is occasionally seen, which may falsely suggest an autonomous adenoma-like lesion.

**Clinical findings**

**Fat distribution**

Centripetal fat deposition is the most common manifestation of glucocorticoid excess and is often the initial symptom of the patient. Although weight gain is classic, it may be minimal. The peculiar distribution of adipose tissue readily distinguishes it from simple obesity: fat accumulates in the face and the supraclavicular and dorsocervical fat pads, resulting in a typical moon face and buffalo hump, which is most often accompanied by facial plethora. Fat also accumulates over the thorax and the abdomen, which becomes protruding (Fig. 1). This acquired habitus change is best evidenced by comparison with anterior photographs.2,3,7

**Protein-wasting features**

Not as frequent, but certainly crucial, are the clinical features that pertain to the protein-wasting effect of chronic cortisol excess. Absent in simple obesity, they have a high diagnostic value and must be thoroughly investigated at examination.2,3,7
Skin thinning due to the atrophy of the epidermis and the underlying connective tissue may be mild and is best appreciated by running the skin gently over the tibial crest; in some patients, the skin is so fragile that it can be scratched simply by removing a strip of adhesive tape. Skin thinning and tension over accumulated fat both account for the plethoric appearance of the face and the purple aspect of striae due to the streaks of capillaries that almost become visible. Striae are present in many patients and are most commonly located on the abdomen and the flanks, and also on the breasts, hips and axillae. In contrast with the usually whitish and small striae often seen after pregnancy or rapid weight gain, the striae of Cushing’s disease are large and purple. Minimal trauma generates multiple ecchymotic lesions or purpura, especially on the forearm, and venous puncture often results in large ecchymotic lesions. Minor wounds heal slowly and are the source of postoperative complications at the incision site. The most superficial wounds, particularly frequent on the lower extremities, may lead to indolent infection and ulceration that take months to disappear. Lower limb oedema is frequent and does not always result from congestive heart failure but rather from increased capillary permeability. Protein wasting is responsible for generalised tissue fragility. Surgeons usually find that the tissues tear easily. Spontaneous ruptures occur, mainly of tendons.

Muscle wasting is frequent and characteristically proximal, leading to fatigability and muscle atrophy, particularly in the lower limbs. The weakness may be so severe as to prevent the patient from getting up from a chair without help.

Bone wasting results in general osteoporosis. The prevalence of bone demineralisation assessed by bone mineral density using dual energy X-ray absorptiometry is about 40%8; particularly vulnerable is the vertebral body. Compression fractures of the spine are evident on plain radiographs in about 20% or 80% of the patients depending on the studies, and almost half of the patients complain of backache. Kyphosis and loss of height, sometimes dramatic, are frequent. Pathological fractures can occur elsewhere, particularly in the ribs and pelvis.8,9

There is an impaired defence mechanism against infections. Banal bronchopulmonary infections may take a most aggressive, life-threatening course. Superficial mucocutaneous infections are extremely frequent, such as tinea versicolor and ungual mycosis, which will only subside with the control of hypercortisolism.
Non-specific features

Most patients have high blood pressure. It may occasionally be severe, inducing cardiac hypertrophy and eventually congestive heart failure. Increased susceptibility to both arterial and venous thrombosis is also present due to lipid and coagulation disturbances. Cardiovascular complications are the major threats of the disease and contribute greatly to its morbidity and mortality rate.

Hirsutism, due to a slight excess of adrenocortical androgens, is extremely frequent in women. Excess adrenal androgens and cortisol both suppress the gonadotroph function, which results in an array of gonadal dysfunctions: most female patients have oligomenorrhea and amenorrhea, and infertility is frequent. In male patients, the curtailed gonadotroph function induces a dramatic fall in testosterone, which is not compensated by the increased adrenocortical androgens. It results in a loss of libido and diminished sexual performance. Loss of sexual hair and reduced testis size are observed.

Psychic disturbances are extremely common. They are highly variable both in their expression and their severity, and they do not correlate with the intensity of the hypercortisolism. They are most often mild and limited to anxiety, increased emotional lability and irritability or unwarranted euphoria. Sleep disorders are also frequent. Severe psychotic symptoms may occur, such as depression, maniac disorders, delusions and/or hallucinations, and may ultimately lead to suicide. Decreased short-term memory and cognition are common and are associated with transient features of brain atrophy that disappears after cure. Impaired quality of life may persist years after control of the hypercortisolism.

The clinical features of chronic hypercortisolism cover a wide spectrum of symptoms and signs. Many of them – such as obesity, high blood pressure and psychological disturbances – are extremely common, and yet Cushing’s syndrome is rarely their cause. Abnormal fat distribution (central obesity) is the most sensitive sign, and evidence of protein wasting (i.e., osteoporosis and myopathy) is highly specific. In the absence of fat redistribution, the likelihood of Cushing’s syndrome is slim; in the presence of protein wasting, weight gain is highly suggestive of Cushing’s syndrome. This scheme provides a most useful guide for the clinical approach of many suspected cases.

Particular combinations of symptoms and signs

Though many patients with Cushing’s disease present with a highly suggestive combination of symptoms and signs, as described above, in other cases the clinical picture is much less clear and even misleading, for reasons cited below.

Some patients exhibit the syndrome only partially, and one symptom can dominate the whole picture. It is not rare that an occasional patient has been misdirected for months or even years in rheumatologic or psychiatric wards before it is realised that he or she has a Cushing’s syndrome. Mild forms may be mistaken for all sorts of ill-defined conditions, such as polycystic ovary syndrome, essential hypertension, idiopathic cyclic oedema and idiopathic hirsutism.

Some patients with Cushing’s disease have a cyclical pattern in which episodes of active hypercortisolism are separated by periods of normal pituitary–adrenal activity of varying lengths. Some patients exhibit a fairly regular pattern of episodic hypercortisolism and complain of ‘swelling’ from time to time. A slight delay in obtaining the necessary blood, salivary or urine samples to establish hypercortisolism explains how the diagnosis may be missed. The simplest way to make this diagnosis is to educate the patient to collect a 24-h or overnight urine sample or bedtime saliva at the time when he/she feels the symptoms have recurred.

In mild forms of Cushing’s disease, the diagnosis is often less apparent in men than in women. It is claimed that some persistent testicular androgens offer better protection against the protein-wasting effect of cortisol.

Cushing’s disease usually presents as a slowly progressive pathologic condition with a mild degree of hyperandrogenism in females.

In rare instances, the first presenting symptoms will be those of a pituitary tumour. The fine biological work-up of a pituitary macroadenoma may clearly indicate a state of ACTH hypersecretion in a patient who had no evident features of chronic hypercortisolism. These findings may even be
secondarily encountered during careful monitoring of what was primarily diagnosed as a non-functional pituitary adenoma, stressing the need for careful and prolonged follow-up of such patients.

In children, Cushing’s disease almost invariably provokes growth retardation if not growth arrest. A decrease in growth rate may be the sole symptom in mild forms of the disease, where the final diagnosis is often delayed. Weight gain with centripetal obesity, as in adults, is present in most cases, however.23,24

Pregnancy rarely occurs in a hypercortisolic woman because of the hypofertility associated with this condition. In mild cases of Cushing’s disease, the clinical diagnosis may be obscured by features frequently present in pregnancy, such as weight gain, high blood pressure, abdominal striae and impaired glucose tolerance. However, the presence of exaggerated morphological changes, hyperandrogenic manifestations and especially catabolic features should raise a suspicion.25–27

**Diagnostic procedures**

**Routine laboratory**

Routine laboratory tests may provide some clue to the diagnosis. None is specific, and their major function is rather to measure the severity of the disease. The test results are not only related to the rate of cortisol secretion, but also for each individual, to his or her personal sensitivity to glucocorticoids. They will be most useful for the follow-up of treated patients.

Altered counts of circulating leucocytes are frequent, showing increased neutrophils and decreased lymphocytes and eosinophils.

Serum electrolytes are usually normal. In severe cases, hypokalaemia, alkaloosis and hypernatraemia develop in response to high levels of cortisol and deoxycorticosterone.1 Renal stones are present in approximately 50% of all patients.28 Although some degree of glucose intolerance is observed in most patients, frank fasting hyperglycaemia occurs in a minority of patients. Hyper-homocysteinaemia and reduced serum folate levels may be observed.29 The adverse metabolic profile is often associated with hepatic steatosis (20% of patients)30 and increased visceral fat.31

Chest X-ray and electrocardiogram results are normal, except in cases of rib fractures, and cardiac enlargement due to high blood pressure. Serum IgG have been reported to be slightly depressed. Bone mass is reduced in many patients,8 as well as biochemical markers of bone formation such as osteocalcin.32–34

**Establishing the hypercortisolic state**

The diagnosis of hypercortisolism should be performed under controlled conditions, avoiding stressful or pathological situations that might create unspecific activation of the pituitary–adrenal axis.

**Baseline measurements**

Three baseline measurements have essentially equivalent diagnostic performances, and can be used alternatively, depending on the local availability.3,35

**Late-night serum cortisol.** As a group, patients with Cushing’s syndrome have high early-morning serum cortisol values, yet around 50% of patients fall within the normal range.

Because patients with Cushing’s syndrome typically lack a normal circadian rhythm, this overlap progressively disappears during the day. Late-evening serum cortisol has a high sensitivity and specificity. A single sleeping midnight serum cortisol of <50 nmol l\(^{-1}\) (1.8 μg dl\(^{-1}\)) effectively excludes Cushing’s syndrome; an awake midnight serum cortisol of >207 nmol l\(^{-1}\) (7.5 μg dl\(^{-1}\)) is highly suggestive of Cushing’s syndrome.3,35

**Late-night salivary cortisol.** Salivary cortisol is a perfect indicator of plasma-free cortisol. It offers a convenient and non-stressful way of sample collection, even in outpatients. It can substitute for plasma cortisol with at least an equal performance, approximately 95% specificity and sensitivity.3,35
24-h urinary cortisol excretion (urinary cortisol). An almost perfect distinction is obtained between patients with Cushing’s syndrome and normal subjects, provided that the urine collection is done accurately and that the laboratory has validated its normal values in a large population of normal subjects (usually less than 250 nmol per 24 h (or 90 μg per 24 h)).

**Suppression tests**

The classic 2-day low-dose dexamethasone suppression test. In a normal individual, the administration of 0.5 mg dexamethasone, given every 6 h for eight doses (2 mg per day for 2 days), induces almost complete suppression of ACTH and of cortisol secretions. Urinary cortisol excretion on the second day (normal response: less than 27 nmol per 24 h (or 10 μg by 24 h)), or morning serum cortisol at the end of the test (normal response: less than 50 nmol l\(^{-1}\) (or 1.8 μg dl\(^{-1}\))) can be alternatively used.

The overnight 1-mg-dexamethasone suppression test. One milligram of dexamethasone is administered orally between 2300 h and midnight, and plasma cortisol is measured the next morning between 0800 h and 0900 h. In normal subjects, serum cortisol values will be suppressed below a definite limit (established by each laboratory, and depending on the assay method), which is usually less than 50 nmol l\(^{-1}\) (1.8 μg dl\(^{-1}\)) for most immunoassays. Although it is convenient, this test has a low specificity, particularly in obese subjects.

Numerous studies have compared these approaches, baseline and dynamics, to conclude that they have essentially quite similar diagnostic performances. The endless game is to move the thresholds of the responses to the tests to reciprocally improve the sensitivity and decrease the specificity, or vice versa. For further in-depth analysis, read the recent reviews.

**Investigating the cause of Cushing’s syndrome**

The classical approach is to distinguish first between ACTH-dependent- and ACTH-independent (adrenal Cushing) causes, using fine evaluation of the baseline corticotroph function; then, in case of ACTH-dependent Cushing, to distinguish between Cushing’s disease and ectopic ACTH syndrome, using both fine dynamic assessment of the corticotroph function and imaging (Fig. 3). These steps are best performed in specialised referral centres.

**Baseline plasma ACTH**

Baseline ACTH plasma levels >2 pmol l\(^{-1}\) (10 pg ml\(^{-1}\)) coincident with hypercortisolism, virtually excludes a primary autonomous adrenocortical tumour. Conversely, undetectable levels (<1 pmol l\(^{-1}\) (5 pg ml\(^{-1}\)), virtually eliminates an ACTH-dependent cause. Borderline values need cautious interpretation, repeat measurements or a CRH stimulation test, as patients with Cushing’s disease and adrenal pathologies may have intermediate values, particularly in their mild forms.

Patients with Cushing’s disease have morning plasma ACTH levels that tend to be slightly elevated. ACTH is almost always measurable (>2 pmol l\(^{-1}\) (10 pg ml\(^{-1}\)). Between one-half and two-thirds of the patients have values within the normal range, and the values of the others usually do not exceed 40 pmol l\(^{-1}\) (200 pg ml\(^{-1}\)).

Patients with the ectopic ACTH syndrome tend to have higher levels of ACTH than patients with Cushing’s disease, yet the overlap between the two groups is wide.

**Dynamics of the corticotroph function**

The high-dose dexamethasone suppression tests. Dexamethasone is dosed as 2 mg every 6 h for 48 h or as a single 8-mg dose at midnight. Most patients with Cushing’s disease (ca. 80%) will suppress urinary or serum cortisol to a value of <50% of the basal level. The high-dose dexamethasone suppression test is typically negative in the ectopic ACTH syndrome.

Direct assessment of the pituitary ACTH reserve. The CRH test. Synthetic ovine or human CRH is administered intravenously (IV), 100 μg or 1 μg kg\(^{-1}\) body weight, and plasma ACTH and cortisol are
measured during the next 60 min. Patients with Cushing’s disease are typically responsive (ACTH and/or cortisol plasma levels increase by more than 50% and/or 20%, respectively) with a sensitivity of about 85% for Cushing’s disease. Patients with the ectopic ACTH syndrome are typically unresponsive.36,39–41

The desmopressin test. The desmopressin test (10 μg IV) induces a positive ACTH response in approximately 85% of patients with Cushing’s disease.42–44 Yet, since the V3 receptor is expressed in as many as 30% of ACTH-secreting non-pituitary tumours,45,46 the usefulness of the desmopressin test is limited in the differential diagnosis of ACTH-dependent Cushing’s syndrome. It is useful in the post-operative assessment of patients with Cushing’s disease.15

Tracking the ACTH source: bilateral inferior petrosal sinus samples

Bilateral inferior petrosal sinus sampling. Bilateral inferior petrosal sinus sampling (BIPSS) allows for the collection of blood draining immediately from the pituitary gland. In difficult cases, this invasive procedure establishes whether ACTH over-secretion is of a pituitary or non-pituitary origin. The diagnostic accuracy of the test requires the administration of CRH. A basal central: peripheral ratio of >2:1 or a CRH stimulated ratio of >3:1 is indicative of Cushing’s disease.47 It has a sensitivity and a specificity of 94%.48

It is an invasive approach that should be reserved for experienced centres, and only in specific situations: if a patient has responses both on dexamethasone suppression and CRH testing, and a typical lesion of 6 mm or more at the pituitary MRI scan, it is reasonable to consider the diagnosis of Cushing’s disease to have been made. In other cases, BIPSS should be discussed.15

Imaging studies

Pituitary magnetic resonance imaging (MRI). Performing MRI of the pituitary has significantly improved our ability to detect pituitary microadenomas in Cushing’s disease (Fig. 2). T1-weighted MRI images
should be obtained in the coronal plane with and without gadolinium DPTA enhancement. A hypo-intense signal better delimited after enhancement is typical of a microadenoma, which can be seen in as many as 60–70% of the patients. In the rare cases with macroadenomas, MRI also helps to detect possible invasion of the cavernous sinus. 15

Adrenal computed tomography scan. As a result of chronic stimulation by excess ACTH, the two adrenal glands develop hyperplasia. On CT scan, the two glands are usually moderately enlarged. There is no reliable measure of the adrenals, but a loss of normal concavity of their borders is considered pathological. Occasional nodules may be present, and macronodular hyperplasia develops in up to 15% of patients with Cushing’s disease.

Pitfalls in diagnosis

Pitfalls in the diagnosis of hypercortisolism

Drug interactions

High oestrogen states, as encountered in pregnancy or with oral contraceptive use, induce increased plasma corticosteroid-binding globulin levels. This modification is accompanied by a concurrent increase in plasma cortisol. Persistence of a normal pituitary–adrenal axis is easily demonstrated by other indices: free plasma cortisol and salivary cortisol are normal and have normal circadian

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**Fig. 3.** Diagnostic flow-chart in a patient with clinical suspicion of Cushing’s syndrome.

**HDD :** High Dose Dexamethasone suppression test  
**BIPSS :** Bilateral Inferior Petrosal Sinus Sampling

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**DEMONSTRATE HYPERCORTISOLISM**

Late night plasma (salivary) cortisol … or  
24-h urinary cortisol excretion… or  
Classic low dose dexamethasone suppression test or  
Overnight 1-mg dexamethasone suppression test

**ESTABLISH ITS CAUSE**

ACTH-dependent?

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**CUSHING’S DISEASE**  
**ECTOPIC ACTH SECRETION**  
**ADRENAL CUSHING**

**YES**  
(Plasma ACTH > 10 pg/ml)

**NO**  
(Plasma ACTH < 5 pg/ml)
variations, and 24-h urinary cortisol excretion is normal. The classic low-dose dexamethasone test is normal on urinary cortisol excretion. In late pregnancy the situation is more complex due to additional factors that profoundly modify the pituitary–adrenal homeostasis (see below).

Anticonvulsants such as phenytoin and barbiturates accelerate dexamethasone metabolism. Subjects on these drugs have false-positive low-dose dexamethasone suppression tests.3

Intercurrent pathological states

Simple obesity was a major diagnostic problem when urinary 17-hydroxycorticosteroids were the standard markers of adrenocortical activity. It has now been amply demonstrated that the more appropriate parameters of baseline cortisol homeostasis (e.g., plasma and salivary cortisol, circadian rhythm and urinary cortisol excretion), and the classic low-dose dexamethasone suppression test are all normal in simple obesity.

Chronic renal failure has been mistakenly associated with abnormal glucocorticoid regulation, including diminished suppressibility by dexamethasone. With the necessary precautions – plasma extraction or highly specific immunoassay, and long enough suppression tests for 2 days – plasma cortisol is normal and normally suppressible by the classic 2 days low-dose dexamethasone test.

Hypercortisolic states without Cushing’s syndrome

Various pathological or physiological conditions may be associated with biochemical, and sometimes clinical, evidence of endogenous glucocorticoid excess. In these situations, increased cortisol production is thought to be driven by pituitary ACTH over-secretion, secondary to a central nervous system disorder or to an appropriate adaptive reaction. This functional hypercortisolic state (“Pseudo-Cushing”) is usually mild and transient – regressing with its cause – and thus is not classically regarded as a cause of genuine Cushing’s syndrome. It has long been recognised and is best studied in depressed patients.1

Depression. Patients with severe endogenous depression often exhibit biochemical stigmata of hypercortisolism: plasma cortisol and urinary steroid excretion are increased, and they do not suppress normally on the classic 2-day low-dose dexamethasone test.

Whatever the exact pathophysiological mechanism, the hypercortisolic state that accompanies depression often creates a serious diagnostic problem. A depressed patient may present with obesity, mild hirsutism, slight hypertension and moderate glucose intolerance. The question is, is he or she a depressed patient with transient functional hypercortisolism, or is he or she a true Cushing’s syndrome patient with secondary depression? Although none of them is by itself absolutely conclusive, several features may more or less distinguish between the two conditions. Classically, in depression, the hypercortisolic state is clinically and biologically mild. Urinary cortisol excretion almost never exceeds 3 times the upper limit of normal; the circadian pattern of plasma cortisol levels is less disrupted and sometimes a mere phase-shift phenomenon is observed; cortisol response to insulin-induced hypoglycaemia is present in depressed patients in contrast to patients with Cushing’s syndrome of any cause, including Cushing’s disease; ACTH response to CRH is attenuated in contrast to the exaggerated response of Cushing’s disease. Yet, a wide overlap is observed; ACTH response to desmopressin is negative and imaging investigations find no evidence of adrenocortical or pituitary tumour. Finally, during follow-up, the disappearance of hypercortisolism with the successful treatment of the depressive state may provide the definitive answer.

Anorexia nervosa. Anorexia nervosa is associated with an array of neuroendocrine disorders, among which sustained hypercortisolism is frequent. Increased urinary cortisol and lack of normal suppression by the classic low-dose dexamethasone test may be found. In contrast, with depressed patients, there is generally no clinical hesitation for the diagnosis.

Alcoholism. Patients with chronic alcoholism may present with clinical and biochemical features of glucocorticoid excess, creating a pseudo-Cushing’s syndrome. The simplest – and most effective – way to avoid a false diagnosis is to consider alcoholism and to observe the remarkable concurrent decrease and normalisation of cortisol indices and liver function tests during alcohol withdrawal in hospitalised patients.
Pregnancy. Normal pregnancy is associated with a profound hormonal turmoil that significantly alters glucocorticoid homeostasis. In the first months of pregnancy, increased oestrogens induce a two- to threefold rise in plasma corticosteroid-binding globulin, which culminates at about 3 months and plateaus thereafter. There is a simultaneous rise in plasma cortisol levels. With time, more significant alterations develop that culminate in the last trimester when unequivocal features of a hypercortisolic state are found, at least from a biochemical point of view. The mean unbound and salivary cortisol and urinary cortisol excretion show a two- to threefold increase. Thirty percent of women have a 24-h urinary cortisol excretion above the upper limit of normal non-pregnant women, and most have an abnormal response to the classic 2-day low-dose dexamethasone suppression test. However, the biochemical abnormalities remain mild, and a normal circadian pattern for plasma and/or salivary cortisol is maintained. 25

Pitfalls in the aetiological diagnosis of Cushing’s syndrome

Cushing’s disease mimicking an autonomous adrenal tumour
In this situation, the suppression tests show little, if any, drop in cortisol secretion, baseline ACTH is marginal and adrenal imaging reveals an apparently unilateral adrenal mass. If a unilateral adrenalectomy is mistakenly performed, hypercortisolism is not resolved and the diagnosis of Cushing’s disease in its macronodular hyperplastic form is secondarily made. To avoid such a mistake, one must very carefully explore and interpret the dynamics of the corticotroph function: the CRH test may show a brisk ACTH response; and a careful examination of the contralateral gland on CT scan shows a hyperplastic gland, and certainly no atrophy. In this rare situation, the doubt can be overcome by Nor-iodocholesterol scintigraphy, which will show an asymmetrical but bilateral uptake.

Severe Cushing’s disease mimicking the classical ectopic ACTH syndrome
The clinical presentation may be severe enough to mimic the classical form of the ectopic ACTH syndrome, with rapid-onset, profound myopathy, severe hypokalaemia and definite hyperpigmentation. In some cases the correct diagnosis may be further obscured by unexpected responses to dynamic tests, such as lack of suppressibility on the high-dose dexamethasone suppression test and/or a lack of ACTH response to the CRH test. In most cases, however, the pituitary imaging will point to the source of ACTH often showing a large macroadenoma. If necessary, and if possible, bilateral inferior petrosal sinus sampling should ultimately provide the unequivocal solution.

Mild ectopic ACTH syndrome mimicking the classic Cushing’s disease
It has become increasingly recognised that some non-pituitary tumours provoke a Cushing’s syndrome with both clinical and biochemical features similar to those of the classic Cushing’s disease. Mild and slowly progressive symptoms are found together with dynamic tests compatible with a non-autonomous, glucocorticoid responsive, ACTH-dependent cortisol overproduction. Although it is quite exceptional, some of these tumours even respond to CRH with an ACTH rise. Because most of these patients have small and indolent bronchial tumours (carcinoids) that may escape the most sensitive imaging approaches, this ‘occult’ ectopic ACTH secretion syndrome can be easily misdiagnosed as Cushing’s disease and even undergo unwarranted, and unsuccessful, pituitary surgery. This is again a situation where the bilateral inferior petrosal sinus sampling is most useful to help the right diagnosis, except in rare cases of concomitant ectopic ACTH–CRH secretion. 49

Treatment
The morbidity and mortality of untreated chronic hypercortisolism demand that Cushing’s syndrome be treated rapidly and actively in most patients.

The goals are to correct adrenocortical over-secretion, to ablate or destroy the primary tumoural lesion with respect to anterior pituitary functions and possibly restore a normal pituitary–adrenal axis, and eventually to reverse the peripheral manifestations of steroid excess.
Trans-sphenoidal pituitary surgery

Prior to surgery, a minority of patients may require being medically prepared so that severe hypertension and/or hyperglycaemia are controlled, and the infected areas eradicated. Under these strict conditions, the trans-sphenoidal approach is considered a safe procedure. Mortality is exceptionally reported as a consequence of meningitis.

A successful surgical outcome of selective adenomectomy or partial hypophysectomy characteristically induces a state of transient (although sometimes lasting up to several years) corticotroph deficiency, during which steroid coverage is necessary. There is general agreement that this brings about a high immediate success rate, between 60% and 80%, in a recent series. It is likely that these variations reflect surgical skill and experience. These encouraging figures must be tempered by the fact that some patients who were immediate successes eventually relapse. It is recommended that all initially cured patients be regularly and indefinitely followed.

Yet there are patients who are unexpected failures either because the exploration could not find the adenoma or because removal of an apparent adenoma does not control the hypercortisolism. The major causes of failure are anatomical, due to the lateral extension, the small size or the inaccessibility of the tumour.

Pituitary irradiation

Conventional radiotherapy has long been used to directly suppress pituitary ACTH over-secretion. Its success rate varies between groups depending on the proposed criteria to define cure. Some groups have reported success rates in the 50% range. Most groups have delivered between 35 and 52 Gy with a daily fractional dose of approximately 200 cGy. Lower dose (20 Gy) has a high relapse rate. The response to radiotherapy is slow, taking months or years for a full effect, and there is a high risk of hypopituitarism.

Other modes of radiotherapy (heavy particles, stereotactic radio-surgery with the gamma knife) are limited to specialised centres. Despite initial enthusiasm for the gamma knife, there is a relapse rate of up to 20% following treatment, which does not compare favourably to conventional radiotherapy. It may, however, be more rapid in onset in efficacy.

Medical treatments towards the pituitary

The PPAR-γ agonist rosiglitazone has proved efficacious in an animal model of Cushing’s disease. Yet, recent studies in patients with Cushing’s disease or the Nelson’s syndrome have been uniformly unsuccessful.

There is evidence that up to 40% of patients with Cushing’s disease respond to the dopamine agonist cabergoline with a normalisation of cortisol production.

The newer somatostatin analogue, SOM-230, directed towards both the type 2 and type 5 somatostatin receptors, reduces ACTH secretion in cell culture models and in culture of human corticotroph tumour cells: the first, uncontrolled, trial in human shows limited results in patients with Cushing’s disease.

Temozolomide, an oral alkylating chemotherapeutic drug used to treat brain tumours such as astrocytoma, was tried successfully in a patient with aggressive Nelson’s syndrome after four cycles of treatment.

Finally, there are preliminary data in an animal model that retinoic acid may cause direct inhibition of ACTH secretion from corticotroph tumours.

Medical treatments for the adrenals

Op’DDD and adrenolytic drug

Among the anti-adrenocortical drugs, Op’DDD (1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)-ethane) has a unique adrenolytic action; it specifically destroys the adrenocortical cortex.
Patients with Cushing’s syndrome almost invariably reduce their cortisol production on Op’DDD. Direct indicators of plasma-free cortisol, such as salivary or urinary cortisol, are the best parameters. Decreased cortisol production is a slow phenomenon that manifests after 1 or 2 months of treatment.

Although Op’DDD is a highly effective adrenolytic drug with unique properties, its use as a sole therapeutic means in Cushing’s syndrome has several limitations. Because of its numerous, rather than serious, side effects, its particular kinetics, and its highly variable bioavailability, necessitates a close and repeated monitoring. Although its efficacy may last for years in a given patient, it is most often only transient. Its best indication is probably when a transient control of hypercortisolism is needed, such as when waiting for the full effect of pituitary irradiation to take place, or when preparing a severely ill patient for pituitary or adrenal surgery.66,72

**Inhibitors of cortisol synthesis**

In contrast with Op’DDD, all of those compounds exert an almost immediate effect on cortisol production. Yet, because they have no adrenolytic action, their long-term benefit in patients with Cushing’s disease is countered by the inevitable increase in ACTH, which may overcome their partial blocking effect.

Metyrapone inhibits 11 ß -hydroxylase, consequently blocking the last step of adrenal steroid biosynthesis in which the biologically inactive 11-deoxycortisol is converted to cortisol. Metyrapone often results in some general side effects such as nausea and dizziness. It increases the secretion of adrenocortical androgens and may result in intolerable worsening of hirsuties in female patients.66

Aminoglutethimide blocks the first step in adrenal steroid biosynthesis. Its frequent side effects are somnolence, dizziness and skin rash. It is no longer available worldwide.66

Ketoconazole, a drug of the imidazole family, inhibits various steps of adrenal and testicular steroidogenesis. Cortisol synthesis is inhibited at the levels of the 20–22-desmolase and 11 beta-hydroxylase. Several studies initiated in the late 1980s have shown the rapid cortisol-lowering action of ketoconazole in patients with Cushing’s disease.66,73

Intravenous etomidate may be considered in situations where rapid control of cortisol levels is required, especially when oral or enteral medications cannot be administrated and sedation is required in critical ill patients.66

**Glucocorticoid antagonists**

RU486 or mifepristone is an antagonist to both the progesterone and glucocorticoid receptors. Although it effectively blocks the action of cortisol, its administration in Cushing’s disease induces an immediate and inescapable pituitary retort with increased ACTH secretion by the corticotroph adenoma, and further rise in cortisol secretion. For this reason, it cannot, at this stage, be routinely proposed as an alternate therapeutic means.66

**Total bilateral adrenalectomy**

The obvious and major advantage of total bilateral adrenalectomy is its unequalled efficiency to control the hypercortisolic state, the effect of which is constant and immediate. The important dogma is to operate on patients who have been prepared, that is, after a significant period of eucortisolic state, most often obtained by pharmacological means. Although it still remains a difficult surgical procedure, its mortality is now almost negligible, and its morbidity is greatly reduced with these precautions, provided it is performed by a skilled and experienced surgical team. Laparoscopic surgery minimises the postoperative discomfort to the patient.66

Adrenalectomised patients will require life-long steroid treatment with glucocorticoids and mineralocorticoids with their unavoidable constraints, need for adaptation, education and risk of acute adrenal insufficiency.

Unexpectedly, some patients resume endogenous cortisol secretion. This may even lead to a recurrence of their hypercortisolism many years after a total bilateral adrenalectomy. This occurrence is not exceptional, being reported in as many as 10% of cases. It is due to the presence of some adrenal rests that have escaped the surgeon’s knife and to accessory glands located in various sites that have re-grown under the stimulatory action of chronically and highly elevated ACTH plasma levels.
After adrenalectomy, one should carefully follow the growth and secretory activity of the pituitary tumour that was at the origin of the disease. Sellar deformations and clinical hyperpigmentation may indeed occur, with increased plasma ACTH levels, which were first observed in the late 1950s, and defined as the Nelson’s syndrome. Currently, however, the tumour could be detected much earlier at a smaller size with a close follow-up using pituitary MRI and ACTH measurements. The prevalence of corticotroph tumour progression after adrenalectomy defined either by the occurrence of an adenoma at MRI, or the growth of a pre-existing adenoma on pituitary MRI reaches 38% at 3 years, and 47% at 7 years, and plateaus thereafter. Risk factors were duration of Cushing’s disease, baseline ACTH plasma level in the year following adrenalectomy and the rate of increase in ACTH plasma levels after adrenalectomy. Pituitary surgery or irradiation could be discussed in relation to a growing pituitary adenoma.

Thus, the high efficacy of adrenal surgery is counter-balanced by several disadvantages. It is reasonable to use it only when pituitary-directed treatments have failed or are contraindicated.

Prognosis

Chronic hypercortisolism per se is the most severe condition with high morbidity and mortality rates. As reported in an older series, it led to death in a majority of untreated patients. Cardiovascular complications were the predominant causes, followed by infections and suicide. Today, cardiovascular and psychiatric complications still remain the major life-threatening complications. The final prognostic of Cushing’s syndrome lies on the severity of the hypercortisolic state and the aggressiveness of the responsible tumour.

The growth potential of the pituitary tumour may be another determinant of the final prognostic. Rare cases of spontaneous cure of Cushing’s disease have been reported, which are thought to result from infarction and/or calcification of a pituitary tumour. In a minority of patients, tumour growth seems to be boosted by bilateral total adrenalectomy, eventually leading to the Nelson’s syndrome. This rare occurrence is unpredictable. It is another argument that points to the pituitary as the more logical and first target when planning therapeutic strategies in Cushing’s disease.

**Practice points**

- Clinical suspicion of Cushing’s syndrome is based on a combination of sensitive (central obesity) and specific (related to protein wasting) signs.
- Measuring baseline cortisol in a 24-h urinary collection, or in blood or the saliva at bedtime, is the easiest and best way to detect hypercortisolism.
- The final diagnosis, and the search of its cause, requires sophisticated hormonal testing and imaging procedures best performed in specialised referral centres.
- Pituitary surgery by the trans-sphenoidal route offers a success rate and quality of cure that undoubtedly designates it as the first-line therapeutic option in patients with Cushing’s disease.

**Research agenda**

There might well be more patients with Cushing’s syndrome than initially and classically thought. Recent studies in populations supposedly at risk (i.e., diabetes, osteoporosis and adrenal incidentalomas) seem to provide unexpectedly high figures for prevalence! If true, we might be confronted with an epidemic of Cushing’s patients – hopefully with mild clinical forms – causing a further difficulty: How to treat mild hypercortisolism? How to assess the benefit of a specific therapeutic action directed against cortisol?
There is a need for (a) biological marker(s) of glucocorticoid action. As endocrinologists we are happy when we succeed in lowering the cortisol, yet the real question is rather what good, if any, have we done by lowering cortisol?

The corticotroph adenoma is an ‘orphan’ pituitary tumour: in contrast with PRL-, GH- and TSH-secreting pituitary adenomas, ACTH-secreting adenomas are not the target of any drug that has convincingly shown its suppressive action.

Little is known on the aetiology of corticotroph adenomas, and its pathogenesis. Thorough investigation in this field is necessary if we hope to develop targeted therapies. This would be a great help, not only to control hypercortisolism but also to treat recurrent, invasive tumours.

Too many drugs directed towards the adrenals means that none has the desirable quality: pharmaceutical industries might not be very enthusiastic about advancing research towards an orphan disease. Yet a drug with strong activity, and good tolerability, to suppress cortisol secretion at the adrenal would be a great progress.

References


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