Recent Advances in Endocrinology and Diabetes



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Chapter 3

Update on the diagnosis and management of Cushing's syndrome

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INTRODUCTION

Cushing's syndrome is the conglomeration of signs and symptoms caused by excessive circulating cortisol and is associated with poor quality of life [1,2], morbidity, and increased mortality [3,4,5]. The hypothalamic-pituitary axis (HPA) consists of hypothalamic release of corticotrophin-releasing hormone (CRH) which stimulates the synthesis and secretion of adrenocorticotropic hormone (ACTH) from corticotrophs of the anterior pituitary. ACTH stimulates the production and secretion of cortisol from the adrenal cortex (**Figure 3.1**).

In endogenous Cushing's syndrome (the focus of this chapter) high cortisol levels result from either autonomous over-production of cortisol from the adrenal cortex or stimulation by excess ACTH from a pituitary or ectopic tumour. Only rarely does it arise from excess CRH release. The best treatment option is tumour-directed surgical excision, but unsuccessful surgery or contraindications to surgery require initiation of drugs to treat the clinical symptoms associated with hypercortisolaemia. This chapter aims to give an

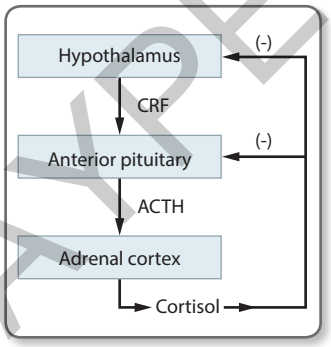

Figure 3.1 Normal hypothalamic-pituitary axis with negative feedback. Cortisol produced in the adrenal cortex will negatively feedback on the hypothalamus and the pituitary and in turn reduce secretion of CRH and ACTH respectively.

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overview of the diagnosis and management of endogenous Cushing's syndrome with some common pitfalls highlighted.

EPIDEMIOLOGY

The prevalence of Cushing's syndrome ranges from 39–79/million. The estimated incidence is 0.2–5.0/million/year [3,6-8]. There is a female-to-male ratio of 3:1 and the median age at diagnosis is 41 years. Approximately 80% of endogenous Cushing's is ACTH-dependent (pituitary or ectopic) and 20% ACTH-independent (primary adrenal) [9].

CLASSIFICATION AND PATHOPHYSIOLOGY OF ENDOGENOUS CUSHING'S SYNDROME

Adrenocorticotrophic hormone dependent (80% of endogenous Cushing's syndrome)

Cushing's disease (60–70%)

Nearly all cases of Cushing's disease are caused by a unilateral pituitary corticotroph adenoma that tends to present in the 3rd-4th decade. Approximately 40% of corticotroph adenomas are not visible on a pituitary magnetic resonance imaging (MRI). Corticotroph hyperplasia rather than adenoma can also cause Cushing's disease, but is very rare. Germline mutations are rare in Cushing's disease but include multiple endocrine neoplasia 1 (MEN-1), aryl-hydrocarbon receptor-interacting protein (AIP) and *CDKN1B* (also known as *p27Kip1*) genes and other cyclin-dependent kinase inhibitor (CDK1) [10]. Somatic mutations in the USP8 deubiquitinase gene in corticotroph adenomas have been shown to cause Cushing's disease via activation of endothelial growth factor receptor signaling [11].

Ectopic adrenocorticotrophic hormone (5–10% of endogenous Cushing's syndrome)

Extrapituitary (ectopic) tumours that secrete ACTH are much less common than Cushing's disease and include benign, occult and malignant neuroendocrine tumours.

Ectopic corticotrophin-releasing hormone

Corticotrophin-releasing hormone tumours leading to excess secretion of ACTH from the pituitary gland are very rare, but include neuroendocrine tumours, phaeochromocytoma and medullary thyroid carcinoma, leading to excess pituitary ACTH secretion.

Pituitary adrenocorticotrophic hormone independent (20–30% of endogenous Cushing's syndrome)

Unilateral adrenal adenomas

These constitute 10–12% of all cases of endogenous Cushing's syndrome and present in the 4th-5th decade. A smaller proportion of unilateral adrenal lesions are malignant and either present in childhood or in the 5th-6th decade and tend to produce a combination of cortisol and androgens.

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Bilateral adrenal

Bilateral adrenal lesions are rare and consist of a collection of pathologies including bilateral macronodular and micronodular adrenal hyperplasia, bilateral adenomas and carcinoma.

Primary bilateral nodular adrenal hyperplasia represents less than 2% of all cases of Cushing's syndrome. Excess cortisol secretion from bilateral macronodular adrenal hyperplasia, despite suppressed ACTH levels, was thought to be an autonomous process, but it has been shown that these hyperplastic adrenal glands display abnormal expression of various hormone receptors that are involved in the control of cortisol production [12]. Interestingly, it has also been shown that corticotrophin can be produced within the adrenocortical tissue and act as a local amplifier of the action of these receptors [13].

A host of germline mutations have been associated with unilateral and bilateral nodular hyperplasia [14,15], but the details are beyond the scope of this chapter.

MORBIDITY AND MORTALITY

Hypercortisolaemia is associated with other medical comorbidities including obesity, diabetes, hypertension, cardiovascular disease, cerebrovascular disease and osteoporosis [16-18]. The immunosuppressive effect of hypercortisolaemia also predisposes to opportunistic infections and impairs natural healing processes [16]. Cushing's syndrome also increases the risk of developing thromboembolic disease such as pulmonary embolism and deep vein thrombosis due to the associated hypercoagulable state [19]. Excess and prolonged cortisol exposure on the brain can lead to psychiatric manifestations such as depression and psychosis and to cognitive dysfunction such as impaired memory [20,21].

Screening for Cushing's syndrome as a secondary cause for some of the aforementioned conditions should be considered, particularly when unexplained, i.e. osteoporosis in a young person with no other risk factors.

Successful treatment of Cushing's syndrome and thereby reversing hypercortisolaemia will improve features of certain conditions, such as bone mineral density and cognitive impairment, but may not achieve remission of these co-morbidities [22,23]. The psychological and physical effects of Cushing's syndrome have a negative effect on overall quality of life in people with the condition [16].

The mortality in Cushing's syndrome is increased compared to the general population with most deaths being secondary to cardiovascular disease. The standard mortality ratio (SMR) in Cushing's syndrome has been calculated to be approximately 2.0–4.0 and although the SMR improves after long-term remission it may not return to a normal SMR [3,8,24-26].

CLINICAL SIGNS AND SYMPTOMS

The clinical presentation of Cushing's syndrome is variable as there is a magnitude of associated signs and symptoms (see **Table 3.1**) that are present in normal people and, therefore getting the diagnosis correct can be very challenging. The most discriminatory features include proximal muscle weakness, pigmented-purple striae, plethora and easy bruising [27]. Weight gain is now as prevalent in the normal population as in Cushing's syndrome and is no longer a useful discriminant. As mentioned, prolonged exposure to hypercortisolaemia can lead to co-morbidities such as osteoporosis, cardiovascular

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Table 3.1 Clinical features of Cushing's syndrome

Presenting symptoms	
• Lethargy	• Headache
• Change in mood and cognition	• Generalised swelling
• Abdominal pain	• Recurrent infections
	• Change in menstrual cycle
Signs on clinical examination	
• Purple striae*	• Round face ('moon face')
• Bruising*	• Dorsal fat pad
• Proximal muscle weakness*	• Hirsuitism
• Plethora*	• Hypertension
• Wasting of the extremities	• Thin skin

*Discriminatory features

disease, thromboembolism, diabetes, psychiatric illness and recurrent illness due to immunosuppression. Individuals with suspected hypercortisolaemia may therefore present to a variety of specialists (e.g orthopaedics, cardiology, gynaecology and neurology) prior to Cushing's syndrome being evaluated as an underlying condition.

INVESTIGATIONS

Initial biochemical screening tests for diagnosis of Cushing's syndrome

Before conducting any biochemical screening exogenous administration of glucocorticoids should be excluded where possible. The endocrine society's clinical practice guideline recommends using two of three screening tests to establish the diagnosis: the 1-mg overnight dexamethasone suppression test, longer-dose dexamethasone suppression test (2 mg/day for 48 h), urinary-free cortisol (UFC) or late night salivary cortisol [28].

Prior to making a decision to perform any biochemical test for establishing the diagnosis it is important to remember that a number of conditions are associated with raised physiological levels of cortisol in the absence of Cushing's syndrome and may therefore result in false positive test results (**Table 3.2**). Pseudo Cushing's refers to physiological over-activity of the HPA axis associated with physical or psychological stress [29]. Pseudo Cushing's syndrome may be seen in patients with anorexia nervosa, depression, alcoholism, obesity and diabetes. If the diagnosis cannot be excluded on clinical grounds then the biochemical screening test should ideally be done once circumstances are optimised, i.e. after treatment of the underlying condition and avoid testing after strenuous exercise or during hospital admission.

The European Endocrine Society highlights the importance of careful clinical evaluation before investigating for Cushing's syndrome and only recommends investigation in the following groups:

1. Those with unusual features for age (e.g. diabetes, hypertension, and osteoporosis)
2. Those with multiple and progressive features, particularly those which are more predictive of Cushing's syndrome
3. Children with decreasing height percentile and increasing weight

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Table 3.2 Causes of physiological hypercortisolaemia with or without clinical features

• Pregnancy • Obesity • Diabetes mellitus • Psychiatric conditions, e.g. depression • Alcohol dependence • Glucocorticoid resistance	• Intense exercise • Malnutrition • Anorexia nervosa • Hypothalamic amenorrhoea • Physical stress, e.g. pain, trauma, surgery • Cortisol-binding globulin excess, e.g. oral contraceptive, PCOS

Table 3.3 Medication that interfere with dexamethasone

Drugs that impair dexamethasone metabolism by inhibition of CYP 3A4 causing false positive results	
Itraconazole	Fluoxetine
Ritonavir	Diltiazem
Aprepitant/fosaprepitant	Cimetedine
Drugs that accelerate dexamethasone metabolism by induction of CYP3A4 causing false negative/normal results	
Phenobarbitol	Rifampacin
Phenytoin	Rifapentine
Carbamazepine	Ethosuximide
Primidone	Pioglitazone

4. Those with adrenal incidentaloma compatible with adenoma, although this is controversial

Overnight dexamethasone suppression test

This test can be done as an outpatient and involves the patient taking 1 mg of dexamethasone by mouth, between 23:00 h and midnight. The patient then attends for a blood test between 08:00 h and 09:00 h the following morning for measurement of serum cortisol. The overnight dexamethasone suppression test assesses whether glucocorticoid negative feedback is normal. The results are normal if the cortisol is less than 50 nmol/L.

False positives or negative results

False positive results can occur if there is an increase in cortisol-binding globulin (CBG) which increases the total serum cortisol, e.g. in a woman on the oral contraceptive pill or hormone-replacement therapy [30]. Dexamethasone is metabolised by the hepatic *CYP3A4* enzyme complex, which is inhibited or stimulated by many commonly used drugs which may result in false positive results or false negative results respectively (**Table 3.3**).

48-hour low-dose dexamethasone suppression test

This test can be done as outpatient with clear written instructions given to the patient. Patients are informed to take 0.5 mg of dexamethasone at 09:00 h on day 1, then at 6 hourly intervals, i.e. at 09:00 h, 15:00 h, 21:00 h and 03:00 h. The patient then attends for a

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blood test at 09:00 h on day 2 to measure serum cortisol. The test is negative (i.e. excludes Cushing's syndrome) if the day 2 (48 h) cortisol is less than 50 nmol/L.

The same precautions for avoiding false positives and false negatives should be taken as for the 1-mg overnight dexamethasone suppression test. False positives result in harm to patients who undergo inappropriate surgery.

Urinary-free cortisol

The test involves the patient collecting their urine in a container over 24 hours. The inconvenience associated with this sometimes leads to incomplete collections and it is therefore useful to measure urinary creatinine and the volume of urine. UFC reflects the integrated tissue exposure to free cortisol over 24 hours and so provides a useful perspective on glucocorticoid physiology that gives different information to the overnight and low-dose dexamethasone suppression tests (LDDSTs). This test needs to be repeated at least twice.

False positive and negative results

In those individuals where there is a suspicion of pseudo Cushing's, the overnight and LDDSTs are a better option to avoid false positive results associated with UFC. UFC can give a false negative result when the glomerular filtration rate is low [31] and false positive result if the urine volume is too low [32], At least two UFC measurement are needed in cases of cyclical Cushing's (intermittent hypercortisolaemia) to avoid false negatives.

Late-night salivary cortisol

The midnight salivary cortisol test can be done at home, as salivary cortisol remains stable at room temperature. The patient collects a saliva sample at midnight using a salivette and then brings it to the laboratory the next day. In healthy individuals the cortisol in both serum and saliva reaches a nadir after going to sleep. The natural circadian rhythm of cortisol is disrupted in Cushing's syndrome which leads to persistently raised cortisol levels even late at night. This test needs to be repeated at least twice.

False positive and false negative results

Immunoassays may increase the false positive rate [33], because of cross-reactivity with cortisone, which the salivary glands convert from cortisol via 11β-hydroxysteroid dehydrogenase type 2 [34]. Salivary cortisol increases with age, hypertension, and diabetes and patients with these conditions may therefore have false positive results [35].

FURTHER INVESTIGATIONS TO ESTABLISH THE CAUSE OF ENDOGENOUS HYPERCORTISOLAEMIA

Serum adrenocorticotrophic hormone measurement

Following a diagnosis of Cushing's syndrome a plasma ACTH level may be useful to distinguish between an ACTH-independent and ACTH-dependent cause. A low plasma ACTH concentration (< 10 pg/mL) is suggestive of an adrenal cause whereas a high ACTH

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concentration (> 20 pg/mL) is suggestive of Cushing's disease or ectopic ACTH secretion. An ACTH value between 10 pg/mL and 20 pg/mL is difficult to interpret [9].

Corticotrophin-releasing hormone stimulation test and high dose dexamethasone suppression test

These tests have a low specificity and should therefore be abandoned [36]. If ACTH-dependent Cushing's syndrome has been confirmed following a LDDST patients can move straight to bilateral inferior petrosal sinus sampling (BIPSS).

Bilateral inferior petrosal sinus sampling

Bilateral inferior petrosal sinus sampling is the gold standard to distinguish between a pituitary versus an ectopic source of ACTH with an approximately 95% specificity and sensitivity [9]. Central blood draining from the pituitary into the inferior petrosal sinus is sampled via a catheter passed into the sinus via the femoral vein. Blood is also taken from a peripheral vein. A central-to-peripheral ACTH gradient of more than two before CRH or desmopressin administration and more than three afterwards confirms a pituitary source. Measurement of prolactin (to normalise ACTH values) in cases without a gradient can confirm successful catheterisation as inability to cannulate the vein could result in false negative results [37,38]. Rare causes such as cyclical ectopic ACTH and CRH-producing tumours could result in false positive results. The drawback of the BIPSS is that it is invasive and relies on skilled interventional radiologists to perform the procedure.

IMAGING

Pituitary imaging

MRI with gadolinium enhancement should be performed in all patients confirmed to have ACTH-dependent Cushing's disease. An MRI with gadolinium will reveal a discrete adenoma in up to 60% of cases [39,40]. It is important to note that approximately 10% of the general population between the age 20–40 years have pituitary incidentalomas demonstrated on MRI [41] and without BIPSS it is possible to wrongly attribute Cushing's to what looks like a pituitary source in a patient with ectopic ACTH.

Further imaging for ectopic adrenocorticotrophic hormone

A full staging computerised tomography (CT) scan or MRI (neck, chest, abdomen and pelvis should be performed). Additionally, a positron emission tomography (PET)/CT or octreotide scan may be considered.

Adrenal imaging

A CT scan or MRI of the adrenals should be performed in confirmed ACTH-independent Cushing's syndrome. If a malignant-looking lesion is detected on initial imaging and androgen levels are raised then further imaging such as ^{18}F-fluorodeoxyglucose (18F-FDG) A PET scan may be considered before open adrenalectomy to document any metastases from an adrenocortical carcinoma.

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MANAGEMENT

A multidisciplinary team (including an experienced endocrinologist) should take the patient's values and preferences into consideration and provide information about the treatment options [42].

TREATMENT FOR CUSHING'S DISEASE (PITUITARY)

Transsphenoidal surgery

The first line treatment of Cushing's disease is transsphenoidal surgery (TSS) by an experienced pituitary surgeon [42]. TSS results remission in 60–90% of microadenomas, and 50–70% of macroadenomas (> 1 cm), depending on local invasion and the experience of the neurosurgeon [43-45]. Remission should be defined by normal ACTH and cortisol circadian rhythms. The risk of late recurrence after presumed curative surgery is estimated to be close to 25% [46]. In those patients with ACTH-dependent Cushing's disease who undergo non-curative surgery, experience late recurrence or for whom surgery is not possible, a shared decision-making approach should be considered as there are several available second-line therapies including repeat TSS, radiotherapy, medical therapy, and bilateral adrenalectomy.

Repeat transsphenoidal surgery

Benefit is observed with repeat TSS in 50–70% of cases, however second and subsequent surgeries are frequently associated with an increased risk of hypopituitarism, diabetes insipidus, and cerebrospinal fluid leak [47,48].

Radiotherapy

Radiotherapy or radiosurgery is recommended in patients who have failed TSS or who have recurrent Cushing's disease. Radiotherapy is also recommended when there are concerns about the mass effects or invasion associated with corticotroph adenomas. Radiotherapy induces remission in the majority of cases, but causes panhypopituitarism in more than 80% of patients [49]. Radiotherapy results in a slow decrease of ACTH levels, delay to remission can vary from between 2 and 3, to 10 years, depending on initial hormone levels. Medical treatment therefore needs to be given after radiotherapy whilst waiting for cortisol levels to normalise. Stereotactic radiosurgery is delivered in a single session. It is theoretically a more precise technique, leading to a lower risk of hypopituitarism. However, the rate of remission is lower, reported in only 50% of cases. Radiosurgery should thus be reserved for small and low secreting lesions [50].

Medical therapies

The aim of medical pharmacotherapeutic agents is to decrease synthesis and cortisol secretion targeting the pituitary gland, adrenal cortex or blocking glucocorticoid receptors. The indications for medical therapy include contraindications to surgery, no adenoma visualised or localised on imaging, while waiting radiotherapy to take an effect or as combination therapy in pituitary carcinomas. None of the available medical therapies achieve a cure, and therapy is often required long-term. An overview of the medical therapies is given below with common side effects listed in **Table 3.4**.

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Table 3.4 Medical therapy options for Cushing's syndrome

Drug and dose regime	Mode of action	Side-effects
Site of action: pituitary		
Pasireotide	Somatostatin analogue (binds to receptor subtypes 1, 2, 3 and 5)	GI symptoms, sinus bradycardia, cholelithiasis **Risk:** hyperglycaemia
Cabergoline	Dopamine receptor subtype 2 agonist	Dizziness, nausea, postural hypotension Possibility of valvular heart disease
Site of action: adrenal cortex		
Metyrapone	Inhibits 11β-hydroxylase	GI symptoms, rash, dizziness, ataxia, hirsutism, acne, oedema, hypertension and hypokalaemia
Ketoconazole	Inhibits several steroidogenic enzymes	GI symptoms, reversible increase in aspartate aminotransferase and alanine aminotransferase, rash, sedation **Risk:** severe hepatotoxicity, hypogonadism in men
Mitotane	Inhibits several steroidogenic enzymes	GI symptoms, neurological effects (dizziness, ataxia, vertigo, decreased memory, confusion), dyslipidaemia **Risk:** potential teratogen and can cause abortion
Etimodate	Inhibiting 11β-hydroxylase and cholesterol sidechain cleavage	Requires monitoring in intensive care unit
Site of action: glucocorticoid receptor		
Mifepristone	Glucocorticoid receptor antagonist	GI symptoms, hypoadrenalism, hypokalaemia, hypertension, irregular menses, endometrial hyperplasia, rash

GI, gastrointestinal.

Adrenocorticotrophic hormone – lowering agents

Cabergoline is a dopamine agonist mainly used for treatment of prolactinomas for tumour shrinkage and reduction in prolactin secretion. Corticotroph adenomas may express dopamine receptors. About 35% of patients treated by high doses of carbergoline for Cushing's disease achieve significant reduction in cortisol levels, but only 30% sustain a long-term effect [51].

Pasireotide is a somatostatin agonist with a particular binding affinity for somatostatin receptor isoforms 1, 2, 3 and 5. Pasireotide is associated with a risk of inducing or worsening pre-existing hyperglycaemia. A double-blind randomised controlled trial showed a significant decrease in cortisol levels in participants with Cushing's disease [52], but the side effects make this a poor choice for patients with Cushing's syndrome.

Steroidogenesis inhibitors

Metyrapone is a pyridine derivative that blocks cortisol synthesis mainly through inhibition of 11β-hydroxylase. It achieves rapid and effective control of hypercortisolaemia in approximately 50% of patients with Cushing's syndrome [53].

Ketoconazole is an antifungal agent with steroidogenesis inhibitor effects linked to inhibition of cytochrome P450 enzymes [54]. It is reported to normalise cortisol levels in Cushing's disease in about 50% of cases. The major concern is hepatotoxicity and liver function tests must be monitored during treatment [55].

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Mitotane is derived from the insecticide dichlorodiphenyldichloroethane (DDD) and inhibits side chain cleavage of cholesterol and also other cytochrome P450 enzymes (11α- and 18-hydroxylase). It has a direct toxic effect on the adrenal cortex. There is a 4-week delay to obtain maximal efficacy due to its accumulation in adipose tissue. Mitotane is primarily used in the treatment of advanced or inoperable adrenocortical carcinoma [56].

Etomidate is an intravenous anaesthetic agent. It inhibits cortisol synthesis by inhibiting CYP11B1 with 11β-hydroxylase activity, and cytochrome P450 at high concentrations. Etomidate is very effective in reducing cortisol levels, but is limited by the fact that it can only be used intravenously in an intensive care unit due to respiratory suppression and sedation [57]. It should therefore be reserved for severe states of hypercortisolaemia.

Glucocorticoid receptor antagonist

Mifepristone is currently the only available glucocorticoid receptor antagonist and is effective in controlling clinical signs of hypercortisolaemia. Drawbacks to its use include its mineralocorticoid mode of action resulting in a high risk of hypokalemia. In addition, there is no biochemical means to monitor the patient because cortisol levels remain unchanged or may rise during treatment [58].

Bilateral adrenalectomy

When hypercortisolaemia is severe or if pituitary surgery fails, then bilateral adrenalectomy can be considered as it resolves cortisol hypersecretion rapidly in the vast majority of cases, with a low risk of perioperative complications particularly when performed via the laparoscopic or retroperitoneoscopic approach [59,60]. In addition, bilateral adrenalectomy can be used as a primary treatment for pituitary Cushing's in selected cases. The major and expected side effect of bilateral adrenalectomy is adrenal insufficiency requiring lifelong replacement of glucocorticoid (hydrocortisone or prednisolone) and mineralocorticoid (fludrocortisone). Nelson's syndrome, which is pituitary tumour progression observed after adrenalectomy, is rare [61].

TREATMENT FOR ADRENAL CUSHING'S SYNDROME

Functional adrenal adenomas causing Cushing's syndrome should be treated with unilateral adrenalectomy [62]. A laparoscopic or retroperitoneoscopic approach is preferable as is it safe, effective and requires less time spent in hospital by the patient, when compared to open adrenalectomy. Glucocorticoid replacement is required post-operatively until the HPA axis recovers. After surgery adrenal cancer can be treated medically with steroidogenesis inhibitors and mitotane [63].

TREATMENT FOR ECTOPIC ACTH SECRETION

The histology of ectopic ACTH-secretory tumours and the presence of metastasis should guide management. Surgical resection should be the primary goal. If full resection is not possible then other options for biochemical and symptom control include tumour-specific chemothereapy, steroidogenesis inhibitors, mifepristone or bilateral adrenalectomy.

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DISCUSSION AND CONCLUSIONS

The diagnosis of Cushing's syndrome is clinically challenging due to its nonspecific clinical features. Nontargeted screening results in large numbers of false positive diagnoses of Cushing's, and deciding who warrants screening is often the first challenge. Once a decision has been made to screen a patient, the second challenge lies in choosing the best combination of investigations to reduce the risk of false positive or false negative outcomes. When interpreting the tests one should not forget that many conditions cause physiological hypercortisolaemia, however distinguishing between Cushing's syndrome and pseudo Cushing's syndrome can be challenge. No test on its own has a 100% diagnostic accuracy and a combination of screening tests should therefore be used.

Once Cushing's syndrome has been diagnosed an ACTH level should be checked to determine whether it is due an ACTH-dependent source or ACTH-independent source (an adrenal source of autonomous cortisol). Surgery remains the mainstay of treatment for Cushing's disease and adrenal adenomas.

A combination of screening and diagnostic tests has enabled a step-by-step approach to establish the underlying cause of endogenous Cushing's syndrome. Surgical treatment remains the mainstay of management whilst the newer medical therapies in Cushing's syndrome are under further clinical evaluation. Due to the many pitfalls in the diagnosis and interpretation of the various tests, patient selection at the point of screening is the most crucial step in making an accurate diagnosis and preventing unnecessary invasive investigations and procedures. The involvement of the multidisciplinary team (surgeons, histopathologists, oncologists, radiologist and endocrinologist, chemical pathologists) throughout is essential for optimising patient care.

Key points for clinical practice

- Do not screen for Cushing's syndrome before a thorough clinical evaluation confirms your suspicion that the patient belongs to a group that warrants screening.
- Discriminatory clinical features of Cushing's syndrome include plethora, proximal muscle weakness, easy bruising and purple striae.
- Select your screening tests based on your patient's specifications to reduce risk of false positives or false negatives.
- Imaging should only be carried out after it has been established whether the underlying cause of Cushing's syndrome is ACTH dependent or ACTH independent due to the high prevalence of pituitary/adrenal incidentalomas.
- Involve the multidisciplinary team early to optimise patient care.

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