CUSHING'S DISEASE: CONTEMPORARY APPROACHES TO DIAGNOSIS AND MANAGEMENT

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Abstract. Cushing's disease is a rare endocrine disorder caused by adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas, resulting in endogenous hypercortisolism through chronic stimulation of the adrenal glands. Patients commonly present with characteristic clinical features, including central obesity, facial plethora, moon facies, and hirsutism. Prolonged cortisol excess is associated with substantial morbidity, affecting multiple organ systems and increasing the risk of cardiovascular and metabolic complications, respiratory disorders, psychiatric disturbances, osteoporosis, and infections. Consequently, Cushing's disease is associated with significantly increased mortality when diagnosis and treatment are delayed. Early recognition and timely therapeutic intervention are essential to improve clinical outcomes and reduce long-term complications. This review summarizes current evidence regarding the clinical presentation, diagnostic evaluation, and management of Cushing's disease, with emphasis on contemporary guideline-based approaches to diagnosis and treatment.

Keywords: Cushing's disease, hypercortisolism, ACTH-secreting pituitary adenoma, transsphenoidal surgery, dexamethasone suppression test.

Introduction

Cushing's disease is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma, which leads to persistent stimulation of the adrenal cortex and excessive cortisol production. Chronic ACTH excess is also associated with bilateral adrenal cortical hyperplasia. Histopathological examination most commonly reveals either basophilic or chromophobic pituitary adenomas, with chromophobic

features being more frequently observed in larger tumors. The estimated prevalence of Cushing's disease is approximately 40 cases per million individuals, with a marked female predominance. ACTH-secreting adenomas account for a relatively small proportion of pituitary tumors, representing approximately 5-12% of all functional and non-functional pituitary adenomas.

The disease is associated with substantial morbidity due to prolonged exposure to elevated cortisol levels. Patients are at increased risk of cardiovascular and metabolic disorders, respiratory complications, psychiatric disturbances, osteoporosis, and recurrent infections, all of which contribute to increased mortality. Importantly, many of these adverse consequences may persist even after successful treatment of hypercortisolism. Therefore, early recognition of Cushing's disease and timely initiation of appropriate therapy are essential for improving long-term outcomes and reducing the burden of disease-related complications [1, 2].

Clinical Presentation

At the time of diagnosis, more than half of patients with Cushing's disease harbor pituitary microadenomas measuring less than 5 mm in diameter, which may be difficult to detect using conventional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI). Only a small proportion of tumors grow large enough to produce mass effects on surrounding structures or cause radiological changes within the sellar region.

The clinical manifestations of ACTH-secreting pituitary adenomas are primarily related to cortisol excess rather than local tumor compression, as most lesions remain small. Consequently, patients typically present with features of hypercortisolism, including progressive weight gain and characteristic redistribution of adipose tissue. Fat accumulation is often concentrated in the central body regions, particularly the abdomen and trunk, and may be accompanied by supraclavicular fullness, dorsocervical fat deposition ("buffalo hump"), and the development of a rounded facial appearance commonly referred to as "moon facies." [4].

In addition to characteristic changes in body fat distribution, patients with Cushing's disease may present with a broad spectrum of clinical manifestations resulting from chronic cortisol excess. Common cardiovascular findings include arterial hypertension and peripheral oedema, particularly involving the lower extremities. Cutaneous manifestations are frequent and may include thinning of the skin, easy bruising, increased capillary fragility, wide violaceous striae affecting the abdomen, thighs, breasts, and flanks, acne, facial plethora, superficial fungal infections, and delayed wound healing. Musculoskeletal complications are also common, with patients often reporting proximal muscle weakness, reduced muscle mass, and persistent fatigue. Long-term hypercortisolism contributes to impaired glucose metabolism, leading to impaired glucose tolerance or type 2 diabetes mellitus.

Skeletal involvement may manifest as osteopenia or osteoporosis, increasing the risk of vertebral compression fractures and, in severe cases, avascular necrosis of the femoral head.

Elevated ACTH concentrations may cause hyperpigmentation of the skin and mucous membranes, particularly in patients with marked ACTH excess. Neuropsychiatric manifestations are common and range from emotional lability and depression to cognitive impairment and, less frequently, severe psychiatric disorders. Reproductive dysfunction may occur, including menstrual irregularities, secondary amenorrhoea, hirsutism, and reduced libido. The clinical presentation of Cushing's disease is highly variable, and many of its features overlap with those of obesity, metabolic syndrome, pseudo-Cushing states, and other causes of ACTH-dependent hypercortisolism. Nevertheless, prolonged exposure to elevated glucocorticoid levels is associated with substantial morbidity and increased mortality, underscoring the importance of timely diagnosis and treatment [5].

Diagnostic Approach

Assessment of endogenous hypercortisolism commonly begins with evaluation of the normal circadian rhythm of ACTH and cortisol secretion. Under physiological conditions, cortisol production follows a diurnal pattern, with peak concentrations occurring in the early morning and the lowest levels observed around midnight. In patients with Cushing's disease, this circadian variation is often lost, resulting in persistently elevated cortisol levels throughout the day and night. Because cortisol secretion is pulsatile, single random measurements have limited diagnostic value, and repeated testing may be required to confirm abnormalities in cortisol regulation.

Measurement of 24-hour urinary free cortisol (UFC) is a widely used screening test for hypercortisolism. UFC reflects the amount of biologically active cortisol excreted in the urine over a full day and provides an integrated assessment of cortisol production. Elevated UFC values, particularly those exceeding two to three times the upper limit of normal, strongly support the diagnosis of Cushing's syndrome. The test can be performed using several analytical methods, including immunoassays, high-performance liquid chromatography (HPLC), and mass spectrometry. To ensure accurate interpretation, adequate urine collection should be verified by assessment of total urine volume and urinary creatinine excretion. Although UFC is useful for detecting cortisol excess, it is not reliable for diagnosing adrenal insufficiency, as low urinary cortisol excretion may also occur in healthy individuals [6].

Late-night cortisol assessment is an important component of the diagnostic evaluation of suspected Cushing's syndrome, as loss of the normal circadian rhythm of cortisol secretion is one of the earliest biochemical abnormalities associated with hypercortisolism. In healthy individuals, cortisol concentrations decline throughout the

day and reach their lowest levels around midnight. In contrast, patients with Cushing's syndrome typically exhibit persistently elevated nighttime cortisol levels.

Measurement of late-night serum cortisol can be performed under controlled conditions, usually during hospitalization, and elevated values may support the diagnosis of endogenous hypercortisolism. However, because serum sampling may be influenced by stress and sleep disruption, late-night salivary cortisol has become a widely accepted alternative. Salivary cortisol reflects the biologically active free fraction of circulating cortisol and can be collected noninvasively in an outpatient setting. Elevated late-night salivary cortisol measured on at least two separate occasions is considered a highly sensitive and specific screening test for Cushing's syndrome. Owing to its convenience, reliability, and strong correlation with serum free cortisol levels, late-night salivary cortisol measurement is currently regarded as one of the preferred first-line tests for the detection of endogenous hypercortisolism [7].

The overnight 1-mg dexamethasone suppression test is widely used as a first-line screening tool for the detection of endogenous hypercortisolism. The test evaluates the integrity of the hypothalamic–pituitary–adrenal axis by assessing the ability of dexamethasone to suppress cortisol secretion through negative feedback mechanisms. In the standard protocol, 1 mg of dexamethasone is administered orally late in the evening, and serum cortisol is measured the following morning. In healthy individuals, dexamethasone suppresses cortisol production to low levels, whereas patients with Cushing's syndrome typically fail to demonstrate adequate suppression. Morning cortisol concentrations above the established diagnostic threshold are considered suggestive of endogenous hypercortisolism and warrant further evaluation. Although the test has high sensitivity, false-positive results may occur in conditions associated with activation of the hypothalamic–pituitary–adrenal axis, including obesity, depression, chronic alcohol use, and other pseudo-Cushing states. Therefore, test results should always be interpreted in conjunction with clinical findings and additional biochemical investigations [8, 9].

Management of Cushing's Disease

The primary goals of treatment in Cushing's disease are to eliminate the source of excess ACTH secretion, normalize cortisol levels, reverse the clinical consequences of hypercortisolism, and minimize the risk of disease recurrence. In patients with larger pituitary tumors, treatment may also relieve mass-related effects, including compression of the optic apparatus and surrounding structures. An additional objective is to preserve normal pituitary function while avoiding treatment-related complications whenever possible.

Management of Cushing's disease requires a multidisciplinary approach and may involve a combination of surgical, medical, and radiotherapeutic interventions. Transsphenoidal pituitary surgery remains the first-line treatment and offers the

greatest likelihood of long-term remission. Medical therapy and radiation treatment are typically reserved for patients with persistent or recurrent disease, those who are not suitable surgical candidates, or as adjunctive therapies while awaiting the effects of radiotherapy. In selected cases of refractory hypercortisolism, bilateral adrenalectomy may be considered as a definitive option for controlling cortisol excess.

Transsphenoidal surgical resection of the ACTH-secreting pituitary adenoma remains the first-line treatment for Cushing's disease, offering the possibility of durable remission in a substantial proportion of patients when performed by experienced pituitary surgeons. However, persistent or recurrent disease occurs in a meaningful proportion of cases, even years after apparently successful initial surgery, necessitating long-term endocrine surveillance [2,10].

Transsphenoidal surgery remains the cornerstone of treatment for Cushing’s disease and is effective in the majority of patients with ACTH-secreting pituitary adenomas. More than 90% of pituitary tumors are amenable to resection through a transsphenoidal approach, with remission rates generally ranging from 60% to 90% for microadenomas and somewhat lower rates for macroadenomas. While conventional microscopic transsphenoidal surgery has long been considered the standard technique, endoscopic approaches have gained widespread acceptance and are increasingly used because of improved visualization and surgical access. Overall, both techniques demonstrate comparable postoperative outcomes. The extent of tumor removal is influenced by several factors, including tumor size, invasion of adjacent structures such as the cavernous sinus, previous medical therapy, and the experience of the operating neurosurgeon. In patients with radiologically occult microadenomas, partial or total hypophysectomy may occasionally be required; however, this strategy is associated with lower remission rates and a greater risk of postoperative hypopituitarism.

Despite favorable initial outcomes, long-term surveillance remains essential because disease recurrence may occur years after apparently successful surgery. Recurrence rates are generally lower in patients with microadenomas than in those with macroadenomas, while younger age and larger tumor size have been associated with an increased risk of recurrent disease [11].

Medical therapy

Medical therapy plays an adjunctive role in the management of Cushing’s disease and is generally reserved for patients awaiting surgery, those with persistent or recurrent hypercortisolism after surgery, individuals undergoing radiotherapy, or patients who are not suitable candidates for definitive surgical treatment. Although transsphenoidal resection remains the treatment of choice, pharmacological therapy can be effective in controlling cortisol excess and reducing disease-related complications. Most currently available medications act by inhibiting adrenal steroidogenesis, thereby decreasing cortisol production. These agents are particularly

useful for preoperative control of hypercortisolism, as well as for patients with unresectable tumors or delayed therapeutic responses following radiotherapy. Commonly used steroidogenesis inhibitors include ketoconazole, metyrapone, aminoglutethimide, mitotane, and etomidate.

Among these therapies, ketoconazole and metyrapone are the most frequently prescribed. Ketoconazole effectively suppresses cortisol synthesis but requires regular monitoring because of potential adverse effects, including gastrointestinal intolerance, hepatotoxicity, and disturbances in gonadal steroid production. Metyrapone is also widely used and may rapidly reduce cortisol levels; however, treatment can be associated with hypertension, dizziness, fatigue, and other dose-related side effects. Careful biochemical monitoring is therefore essential to optimize treatment efficacy and minimize complications [6].

Cardiovascular and Metabolic Consequences

Chronic glucocorticoid excess exerts profound effects on cardiovascular and metabolic health, including visceral adiposity, insulin resistance, dyslipidaemia, hypertension, and a prothrombotic state, all of which contribute to an elevated risk of cardiovascular events that may persist even after biochemical remission is achieved. A review published in JAMA in 2023 emphasised that cardiovascular risk factors frequently do not normalise completely following successful treatment, supporting the recommendation for sustained cardiovascular risk management in patients with both active and treated Cushing's disease [3].

Bone health represents an additional area of concern, with glucocorticoid-induced osteoporosis and an increased risk of vertebral fractures documented even in patients with mild or subclinical hypercortisolism. Case reports describing multiple fragility fractures in patients with difficult-to-treat Cushing's disease illustrate the severity of skeletal involvement that can occur in inadequately controlled disease, reinforcing the importance of early diagnosis and effective biochemical control [12].

Conclusion

Cushing's disease remain among the most challenging diagnoses in endocrinology, owing to insidious onset, overlap with common metabolic conditions, and the complexity of the diagnostic pathway required to confirm hypercortisolism and localise its source. Advances over the past five years have refined screening strategies, improved the accuracy of dynamic testing for ACTH-dependent disease, and expanded the range of pharmacological options available for patients with persistent or recurrent Cushing's disease following pituitary surgery. Nonetheless, transsphenoidal surgery remains the cornerstone of curative treatment for Cushing's disease, and long-term surveillance for recurrence, as well as for residual cardiovascular, metabolic, and skeletal morbidity, remains essential even after apparent biochemical remission.

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