Cushing's Syndrome: Addressing Diagnostic Delays and Treatment Gaps

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> Cushing's syndrome, a rare endocrine disorder characterised by prolonged exposure to excessive cortisol, presents a significant clinical dilemma due to its varied and often non-specific symptomatology. This diagnostic complexity frequently results in substantial delays between symptom onset and definitive diagnosis, impacting patient prognosis and increasing morbidity. Addressing these diagnostic and treatment gaps is critical for improving patient care, a key theme highlighted at endo 2026.

KEY TAKEAWAYS

- The Pivot: Cushing's syndrome diagnosis often faces delays of 2 to 6 years, hindering timely intervention.
- The Data: Early diagnosis and treatment initiation correlate with improved long-term outcomes and reduced comorbidity burden.
- The Action: Clinicians should maintain a high index of suspicion for Cushing's syndrome in patients presenting with multiple, seemingly unrelated symptoms.

Cushing's syndrome, a condition arising from chronic glucocorticoid excess, manifests with a broad spectrum of clinical features, including central obesity, hypertension, diabetes mellitus, muscle weakness, and psychiatric disturbances. The insidious onset and non-specific nature of these symptoms frequently lead to misdiagnosis or delayed diagnosis.1 Studies indicate that the average time from symptom onset to diagnosis can range from 2 to 6 years, during which patients experience progressive deterioration in health and quality of life.1 This diagnostic lag is compounded by the rarity of the condition, leading to a lower index of suspicion among general practitioners and specialists alike. The endo 2026 conference underscored the urgent need for enhanced awareness and streamlined diagnostic pathways to mitigate these delays.

The diagnostic process for Cushing's syndrome typically involves a multi-step approach, beginning with screening tests to confirm hypercortisolism, followed by tests to determine the aetiology. Initial screening tests include 24-hour urinary free cortisol (UFC) measurement, late-night salivary cortisol, and the overnight dexamethasone suppression test (ONDST).2 A UFC level greater than 150 nmol/24h, a late-night salivary cortisol level greater than 3.6 nmol/L, or a serum cortisol level greater than 50 nmol/L after 1 mg dexamethasone are indicative of hypercortisolism.2 Once hypercortisolism is confirmed, plasma ACTH levels differentiate between ACTH-dependent and ACTH-independent causes. ACTH-dependent Cushing's syndrome, accounting for approximately 80% of cases, is most commonly due to a pituitary adenoma (Cushing's disease).3 ACTH-independent causes are typically adrenal in origin.3 Further differentiation of ACTH-dependent causes often involves imaging studies, such as pituitary MRI, and potentially inferior

petrosal sinus sampling (IPSS) to distinguish between pituitary and ectopic ACTH production. The choice of diagnostic tests and their sequence depends on the clinical context and the pre-test probability of the disease, requiring careful interpretation by experienced endocrinologists. Patient populations at higher risk, such as those with poorly controlled hypertension and diabetes alongside other classic features, warrant a higher index of suspicion and earlier screening.

Treatment Strategies and Outcomes

Treatment for Cushing's syndrome is primarily directed at normalising cortisol levels and addressing the underlying cause. Surgical resection of the tumour, whether pituitary, adrenal, or ectopic, is the preferred first-line therapy. Transsphenoidal surgery for pituitary adenomas achieves remission rates of 70% to 90% in experienced centres.4 Adrenalectomy is curative for adrenal adenomas.5 In cases where surgery is not feasible, unsuccessful, or contraindicated, medical therapies play a crucial role. These agents target various steps in the cortisol synthesis pathway or block glucocorticoid receptor action. Medications include steroidogenesis inhibitors (e.g., ketoconazole, metyrapone, osilodrostat), neuromodulators of ACTH secretion (e.g., pasireotide), and glucocorticoid receptor blockers (e.g., mifepristone).6 Ketoconazole inhibits several cytochrome P450 enzymes involved in steroidogenesis, while metyrapone blocks 11²hydroxylase. Osilodrostat, a newer agent, specifically inhibits 11²hydroxylase, reducing cortisol synthesis. Pasireotide, a somatostatin analogue, acts on pituitary somatostatin receptors to suppress ACTH secretion. Mifepristone, a glucocorticoid receptor antagonist, blocks the effects of cortisol at the tissue level.

The long-term prognosis for patients with Cushing's syndrome is significantly influenced by the timeliness and effectiveness of treatment. Untreated or inadequately treated Cushing's syndrome is associated with increased mortality, primarily from cardiovascular events, infections, and thromboembolism.7 Normalisation of cortisol levels post-treatment can lead to resolution or improvement of many comorbidities, including hypertension, diabetes, and osteoporosis. However, some complications, such as cognitive dysfunction and psychiatric symptoms, may persist even after biochemical remission.7 The importance of early intervention cannot be overstated; prompt diagnosis and initiation of appropriate therapy are directly linked to improved patient survival and reduced long-term morbidity.7

Despite advancements in diagnostic tools and therapeutic options, challenges remain. The heterogeneity of clinical presentation and the need for specialised endocrine testing contribute to diagnostic delays. Furthermore, even after successful treatment, patients require lifelong follow-up to monitor for recurrence and manage residual comorbidities. The endo 2026 discussions emphasised the need for greater awareness campaigns among primary care physicians and the development of clear referral pathways to endocrinology specialists to expedite diagnosis and treatment initiation. Future research should focus on identifying novel biomarkers for earlier detection and developing more targeted and tolerable medical therapies. A significant limitation in current practice is the lack of a single, highly sensitive and specific screening test, often necessitating multiple tests and expert interpretation, which can prolong the diagnostic journey. The psychological burden on patients during this period of uncertainty and illness progression also warrants greater attention.

For extended exploration of endocrine diseases, their intricate diagnostics, and treatment approaches, we recommend the comprehensive Oxford Handbook of Endocrinology and Diabetes.

CLINICAL IMPLICATIONS

The persistent diagnostic delay in Cushing's syndrome, often extending years, represents a significant failure in our current clinical approach. General practitioners and specialists must cultivate a heightened index of suspicion for this rare but devastating condition. When a patient presents with a constellation of seemingly disparate symptoms like new-onset hypertension, unexplained weight gain, and mood changes, Cushing's syndrome should be on the differential, not an afterthought. Relying solely on overt signs like a 'moon face' or 'buffalo hump' means missing too many patients in the earlier, more treatable stages of the disease.

The industry has a role to play beyond developing new therapies. Educational initiatives, perhaps funded by companies with treatments like osilodrostat or pasireotide, could significantly improve early recognition. These efforts should target primary care and non-endocrine specialists, providing practical algorithms for screening and referral. The current reliance on specialist-led diagnosis, while necessary for complex cases, inadvertently contributes to delays when initial suspicion is low in the broader medical community. Streamlined access to diagnostic tests, particularly late-night salivary cortisol, could also reduce the burden on patients and primary care.

Ultimately, the patient bears the brunt of these delays, enduring progressive deterioration in health and quality of life. The long-term sequelae, even after successful treatment, highlight the irreversible damage that prolonged hypercortisolism can inflict. Improving outcomes for Cushing's syndrome patients is not just about new drugs; it is fundamentally about earlier detection and intervention. This requires a collective shift in clinical mindset, moving from reactive management of advanced disease to proactive screening based on a broader understanding of its subtle presentations.

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