



Challenges in Diagnosis and Management of Cushing's Disease

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Cushing's syndrome, first described by Harvey Cushing in 1912, remains a clinical diagnosis based on the presentation of a constellation of symptoms and signs driven by pathological hypercortisolism.¹ Biochemical and radiological investigations serve to confirm and localize the driver of glucocorticoid excess, thus enabling appropriate treatment.

Cushing's disease, which is a specific entity of Cushing's syndrome, is caused by adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas and remains the most common cause of endogenous Cushing's syndrome, accounting for nearly 70% of cases in the adult population.

Several challenges exist in the diagnosis and treatment, including the wide spectrum of phenotype at presentation, when to screen amidst the rising worldwide prevalence of obesity and type 2 diabetes, the widespread use of exogenous glucocorticoids in medicine, problems of choosing the ideal biochemical screening tests, the rise in incidentalomas on imaging, the difficulties in accessing certain radiological modalities for localization studies, lack of easy access to experienced neurosurgical units, and unavailability of novel modalities of radiotherapy as well as pharmacotherapy in certain areas.

Although Cushing's can present with mild features, thus posing a diagnostic challenge, its progressive natural history means these tend to become more severe and numerous over time. Indicative features of hypercortisolism, which are unusual for the patient's age or background population, increases the pretest probability of Cushing's, and in children, a delayed puberty or increased weight with growth slowing is often seen.² Furthermore, difficulty has arisen over when to screen for Cushing's in obese population with

type 2 diabetes, given its prevalence is estimated to be up to around 9% in this setting.^{3,4}

Current Endocrine Society guidelines recommend first- and second-line biochemical screening tests should be undertaken once exogenous glucocorticoid exposure has been excluded and if the pretest probability of Cushing's is high. Initial tests include urine free cortisol (UFC) (at least two measurements), late-night salivary cortisol (LNSC) (two measurements), 1 mg overnight dexamethasone suppression test (ODST), or longer low-dose dexamethasone suppression test (LDDST) in certain populations.⁵ However, there remains debate over which of these tests are the most accurate to diagnose Cushing's.

As each of these tests depends upon different underlying physiological abnormality of cortisol secretion, they do complement each other. However, each has its caveats with accompanying confounding factors: timing and volume of the UFC is crucial, with overcollection leading to false-positive results and undercollection resulting in false-negative results, like in stage IV or V renal failure.⁶ The ODST relies on patient compliance with dexamethasone and timing of the testing. False-positive results can be seen with either rapid or delayed dexamethasone absorption, although measuring concomitant serum dexamethasone levels can help minimize the risk of misdiagnosis. LNSC has the benefit of measuring free cortisol, which may be of use in women taking oral contraceptive agents in whom serum cortisol values can be falsely elevated due to raised corticosteroid-binding globulin, but conversely LNSC values can be abnormal and less helpful in shift workers.⁷

In choosing the best initial test, these factors should be taken into account, as well as the sensitivity and specificity of

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each test. A meta-analysis by Galm et al looked at 139 studies to determine the accuracy of one or more diagnostic tests, including the ODST, LDDST, UFC, LNSC, midnight serum cortisol, and the dexamethasone-suppressed corticotropin-releasing hormone (dex-CRH) stimulation tests. They found that all these diagnostic tests for Cushing's were highly sensitive and specific. However, the ODST was found to be the most sensitive (98.6%), while abnormal LNSC was thought to be most specific. In other words, a normal ODST can be extremely helpful in ruling out the disease, while an abnormal LNSC can be particularly helpful in ruling in the disease.⁸

Hypercortisolism can also be found in other conditions not associated with pathological Cushing's ("pseudo-Cushing's"), including pregnancy, alcoholism, uncontrolled diabetes mellitus, psychiatric disorders, pain, obstructive sleep apnea (OSA), extreme obesity, and glucocorticoid resistance syndromes. Physiologically elevated cortisol levels may or may not exhibit clinical features and there can be overlap with Cushing's features, including hypertension, type 2 diabetes mellitus, weight gain, myopathy, and striae, making diagnosis of true Cushing's challenging.⁹ Therefore, care must be taken in interpretation of the clinical and biochemical findings in these situations. Usually, in nonpathological hypercortisolism, the biochemical hypercortisolism is less marked, the symptoms/signs are nonprogressive, and managing the underlying condition (e.g., pain or OSA) normalizes the cortisol levels. Further difficulties remain in diagnosing Cushing's if it is cyclical in nature, where multiple measures of UFC over time may help make the diagnosis.

Magnetic resonance imaging (MRI) remains the imaging method of choice for detecting ACTH-secreting pituitary adenomas. However, with the standard 1.5T MRI, only approximately 50% of microadenomas are identified.¹⁰ Localization in ACTH-dependent Cushing's can also pose an added challenge to distinguish between Cushing's disease and ectopic ACTH secretion. Given the burden of up to 20% of nonfunctioning pituitary incidentalomas, the Consensus Statement on Diagnosis and Complications of Cushing's Syndrome suggests 6mm as a reasonable cutoff for a pituitary lesion detected by MRI to be considered a corticotrope adenoma, providing a definitive diagnosis and not requiring further evaluation in the presence of dynamic biochemical studies compatible with Cushing's disease.¹¹ When an adenoma is below this size, or when no lesion is identified, bilateral inferior petrosal sinus sampling (IPSS) is the gold-standard test, with sensitivity and specificity reaching 100% with CRH. Other tests such as the high-dose dexamethasone test and CRH test lack sensitivity and specificity to distinguish between pituitary and ectopic source of ACTH. A global challenge remains accessing IPSS service with an interventional radiologist who is experienced in the procedure, including successful sinus cannulation, and therefore it is available in a limited number of centers worldwide. Furthermore, the procedure is also invasive and requires the patient to have hypercortisolism at the time of testing to avoid misleading results, which are added challenges.

Newer, less invasive, modalities are emerging in this field. Novel molecular imaging, utilizing positron emission tomography-computed tomography (PET-CT) with gallium-68-tagged CRH, has been used successfully to delineate corticotropinoma in a study of 27 patients, providing the surgeon with valuable information for intraoperative tumor navigation and also helping to differentiate a pituitary from an extrapituitary source of ACTH-dependent Cushing's.¹²

The clinical care of patients with Cushing's disease requires a multidisciplinary team, working in tandem to deliver optimal care. The remission rates reported for intrasellar microadenomas are 88 to 92%, although recurrent Cushing's is a major problem, with overall rates being reported up to 30%. The debate then is how to approach these patients with options being recurrent pituitary surgery, radiation therapy, medical therapy, and bilateral adrenalectomy. Recurrent pituitary surgery requires a well-experienced neurosurgeon and carries a high risk of hypopituitarism (~30%). Not all tumors are surgically accessible either. There are several advancements in techniques of radiotherapy over the years, but lack of availability as well as lack of head-to-head trials comparing different modalities of radiotherapy makes it difficult for the clinicians. Most drugs used as medical therapy for Cushing's are not FDA-approved yet (e.g., ketoconazole, metyrapone, etomidate, cabergoline). Some drugs that are FDA-approved in this context, such as pasireotide and osilodrostat, carry significant cost burden and not all patients can afford it.¹³ Bilateral adrenalectomy has surgical complication rate of 4 to 20% and the risk of Nelson's syndrome is quite high (8–25%); hence, it should only be reserved as the last line of treatment.⁷

Adding to the troubles, COVID-19 has caused significant disarray to the pituitary services, limiting access to biochemical and radiological testing and also impacting the ability to safely undertake pituitary surgery.¹⁴

The challenges in the context of Cushing's disease as entailed earlier are beautifully highlighted in the survey from the MENA (Middle East and North Africa) region, carried out recently by Beshyah et al.¹⁵ Among the responders, 80 were adult endocrinologists and 8 were pediatric endocrinologists. Majority of them (71.6%) were working at a senior level. The preferred initial screening test was either ODST or UFC, with very few choosing LNSC. Only 47.6% of the responders reported that IPSS was readily available, with 22.6% of them saying it is not available to them at all. There was not much dichotomy in terms of choosing primary treatment, which was pituitary surgery. When asked about the success rate in treating ACTH-dependent Cushing's disease in their respective country of residence, 43.7% reported a success rate of 31 to 50%, and 34.5% reported higher success rate, between 51 and 70%. Ketoconazole was the predominant reported choice for recurrent disease, with a quarter of them reporting that stereotactic radiotherapy was not available to them and more than half of them did not have access to pasireotide. This survey highlights the regional variations in diagnosing tools and treatment modalities for patients with Cushing's disease. This could be related to the lack of availability of certain tests, biochemical and radiological. Paucity of

neurosurgeons with high-volume pituitary surgery can also impact upon the course of management of patients with recurrent disease/relapse, as well as the availability of stereotactic radiotherapy and novel pharmacotherapy.

In summary, Cushing's syndrome continues to pose challenges to the medical fraternity. Shrewd clinical skills remain the cornerstone for diagnosis along with appropriate screening tests. It should be considered when a patient presents with relevant signs and symptoms that occur in a short span of time or when the symptoms and signs are progressively worsening. Access to IPSS as well as the availability of established neurosurgical units remains a challenge. Newer tools such as hair cortisol measurements and PET-CT with gallium-68-tagged CRH appear promising. However, inequalities in accessibility to various tests and treatment options are likely to be present globally in the foreseeable future, thus making Cushing's disease an ever-elusive pathology for clinicians.

Author's Contribution

Both the authors contributed equally.

Compliance with Ethical Principles

No ethical approval is required.

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Conflict of Interest

None declared.

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