Chapter 65

Cushing's Syndrome: Challenges in Diagnosis and Management

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ABSTRACT

Endogenous hypercortisolism is characteristically a condition that should be diagnosed and treated in tertiary care centers with the participation of several specialists. Cushing's syndrome represents the clinical expression of a prolonged exposure to glucocorticoids, independent of its origin. The term Cushing's disease refers to the hypercortisolism that results from the excessive secretion of corticotropin (ACTH) by a pituitary microadenoma. The mechanisms that give rise to the different forms of hypercortisolism are complex and a precise differential diagnosis is one of the major challenges in modern endocrinology. This review focuses on the challenges in the diagnosis and management of Cushing's syndrome.

INTRODUCTION

Cushing's syndrome is a disorder that reflects prolonged and inappropriately high exposure of the tissues to the glucocorticoids, irrespective of the source. While the most common cause is iatrogenic which goes unreported, endogenous Cushing's syndrome once thought to be uncommon, with an incidence of 2–3 per million population per year is now considered an underestimate.[1-4] This article will briefly review the consensus, protocols in diagnosis and management, along with the challenges and limitations.[5-8]

ETIOLOGY AND PATHOPHYSIOLOGY

Excess cortisol production, the biochemical hallmark of endogenous Cushing's syndrome may be caused by either ACTH secretion (from a pituitary or other ectopic tumor) or independent adrenal production of cortisol **(Table 1)**.

TABLE 1 | Classification of causes of Cushing's syndrome

Adrenocorticotropic hormone (ACTH)-dependent causes:

- Cushing's disease (pituitary dependent) 70%
- Ectopic ACTH syndrome 5–10%
- Ectopic corticotropin releasing hormone (CRH) syndrome (rare)
- Macronodular adrenal hyperplasia < 5%
- Iatrogenic (treatment with 1–24 ACTH)

ACTH-Independent causes:

- Adrenal adenoma (10%) and carcinoma (5–10%)
- PPNAD* and Carney's syndrome < 5%
- McCune Albright syndrome (rare)
- Aberrant receptor expression [GIP, IL-1b (rare)]
- Iatrogenic (cortisone therapy)

Pseudo-Cushing's syndromes:

- Alcoholism
- Depression
- Obesity
- PCOS

* PPNAD, Primary pigmented nodular adrenal hyperplasia.
Abbreviations: GIP, Gastric inhibitory polypeptide; PCOS, Polycystic ovary syndrome

CLINICAL FEATURES

Although Cushing's syndrome is clinically unmistakable when the disease is fully manifested, it remains challenging in the mild cases. The classical features originally described by Harvey Cushing—centripetal obesity, moon face, hirsutism and plethora—are seen only in florid Cushing's syndrome. However this gross clinical picture is not always present and a high index of clinical suspicion is required.

Features that best discriminate Cushing's syndrome are the easy bruising, facial plethora, proximal myopathy and the purple striae of more than 1 cm width.[9-11] Predominantly, these are all the signs of protein wasting which are very specific for Cushing's syndrome. Weight gain and centripetal obesity are the most common signs of Cushing's syndrome. In addition to the centripetal obesity, fat deposition occurs in areas like thoracocervical spine, supraclavicular region, cheeks and the temporal regions, giving rise to the rounded moon facies.

Hypercortisolism results in the thinning of the skin and as a result, there is easy bruising and plethoric appearance over the face. The typical striae are frequently found over the abdomen, upper thighs, breasts and arms. These should be differentiated from the less pigmented and paler striae that are seen with pregnancy and rapid weight loss. Presence of skin pigmentation is a strong clinical indicator to suspect ACTH-dependent Cushing's syndrome.

Unexplained osteoporosis with increased tendency for fractures is another sign of protein wasting.

The presence of the above discriminatory features helps us to suspect and to work up further. They also help us to differentiate true Cushing's state from pseudo-Cushingoid states like depression, obesity, alcoholism and metabolic syndrome with or without hypertension and diabetes. Clinical features which are more common in exogenous Cushing's syndrome are glaucoma, cataract, benign intracranial hypertension, pancreatitis and avascular necrosis of the head of the femur **(Table 2)**.

TABLE 2 | Overlapping conditions and clinical features of Cushing's syndrome[7]

A. *Features that best discriminate Cushing's syndrome*

Easy bruising
Proximal myopathy
Facial plethora
Red purple striae (> 1 cm)
In children, weight gain with decreasing growth velocity.

B. *Clinical features that are common and/or less discriminatory*

Symptoms	Signs	Overlapping conditions
Depression	Dorsocervical fat pad	Hypertension
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Supraclavicular fullness	Vertebral osteoporosis*
Back pain	Thin skin*	Polycystic ovary syndrome (PCOS)
Changes in appetite	Peripheral edema	Type 2 diabetes mellitus (DM)*
Less concentration	Acne	Hypokalemia
Decreased libido	Hirsutism	Kidney stones
Impaired memory	Poor healing	Unusual infections
Insomnia Irritability Menstrual abnormality		
Children slow growth	Children—abnormal genital virilization Children—short stature Pseudoprecocious or delayed puberty	

* Cushing's syndrome is more likely if onset of this feature is at a young age.

INVESTIGATION OF PATIENTS WITH SUSPECTED CUSHING'S SYNDROME

Before screening for Cushing's syndrome, we need to be aware that pseudo-Cushing's syndrome is a state where there is overactivity of the hypothalamic pituitary axis without true Cushing's syndrome. Sometimes these may produce results suggestive of hypercortisolism, abnormal dexamethasone suppressibility and mild elevation of urinary free cortisol (UFC).[12] The test of choice that can be used to differentiate true from pseudo-Cushing's syndrome is dexamethasone suppression followed by the CRH stimulation. Patients with pseudo-Cushing's syndrome do not respond to CRH stimulation, while patients with true Cushing's syndrome have a stimulated cortisol value of more than 1.4 µg/dL.[13]

As exogenous Cushing's syndrome is more common than the endogenous one, exclusion of this condition is very important. Apart from the history, basal 8:00 AM cortisol value will differentiate the exogenous from the endogenous Cushing's syndrome. A suppressed cortisol value with Cushingoid features suggests exogenous cause except for cyclical Cushing's syndrome which can be suppressed sometimes. Following are the various tests for screening **(Table 3)**.

Challenges and Limitations of Screening Tests

Following are the challenges and limitations of screening tests:

- Pseudo-Cushing's syndrome and exogenous Cushing's syndrome need to be ruled out before the confirmation of true Cushing's syndrome. Discriminatory features help to differentiate pseudo-Cushing's syndrome clinically, and biochemically by the dexamethasone-CRH test **(Flow chart 1)**.
- Physician ordering the tests must be aware of the collection methods and various assays that are available. The interpretation of the results depends upon the assay used and the local laboratory calibration.[14]
- These assays differ widely in their accuracy and the values near the cut off value close to the functional limit of detection should be interpreted carefully as precision deteriorates at the lower levels.
- There are many drugs and conditions which can interfere with the measurement of cortisol and while interpreting, the physician should be aware of these limitations. Drugs like estrogen containing pills, increase cortisol binding globulin and thereby cause false positive results.[15]
- Sensitivity and specificity of the various tests depend upon the cutoff value that was taken.
- In case of any equivocal results, rescreening is required after 6 months.
- Corticotrophin releasing hormone test may not be feasible due to nonavailability and enormous cost.

INVESTIGATING THE CAUSE OF CUSHING'S SYNDROME

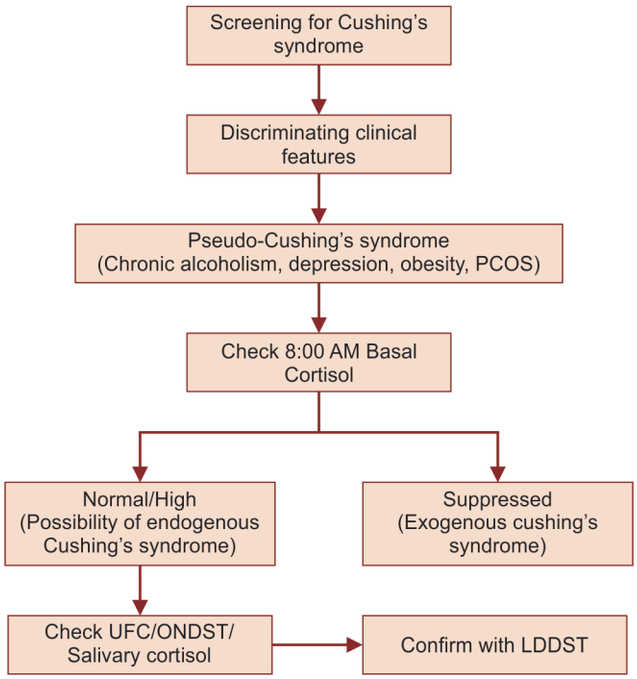
In the investigation of the cause of Cushing's syndrome after establishing hypercortisolism, the initial step is to differentiate ACTH from the non ACTH dependent Cushing's syndrome. And once ACTH-dependent Cushing's syndrome is confirmed, it has to be differentiated further whether pituitary or ectopic.

TABLE 3 | Screening tests

Test	Method	Value	Sensitivity	Specificity	Comments
ONDST	1 mg dexamethasone the night before collection	> 1.8 µg/dL	98–100%	88%	Easy to perform on OP basis
UFC	24-hour urine collection	> 100 µg/24 hours	95–100%	90–95%	More than four times upper limit suggests Cushing's syndrome
Salivary cortisol	Midnight saliva	> 0.27 µg/dL (midnight)	100%	96%	Convenient and nonstressful
Midnight cortisol	Midnight serum	> 7.5 µg/dL (awake)	94%	100%	Stress free sample—a problem
LDDST	0.5 mg dexamethasone for 48 hours	> 1.8 µg/dL	98–100%	97–100%	Used to confirm Cushing's syndrome

Abbreviations: LDDST, Low-dose dexamethasone suppression test; ONDST, Overnight dexamethasone suppression test; UFC, Urinary free cortisol
Two screening tests are recommended for confirming hypercortisolism taking into consideration their sensitivity and specificity as also the availability.

Flow chart 1: Algorithm for screening for Cushing's syndrome



Abbreviations: LDDST, Low-dose dexamethasone suppression test; ONDST, Overnight dexamethasone suppression test; PCOS, Polycystic ovary syndrome; UFC, Urinary free cortisol

Measurement of ACTH

Adrenocorticotropic hormone measurement will help us to differentiate ACTH from the non-ACTH-dependent Cushing's syndrome. Sample is collected with adequate precautions in the morning at 9:00 AM and measured. Some centers advocate checking the ACTH in the midnight along with the cortisol to interpret and differentiate the two. Morning ACTH value of less than 10 pg/ml is suggestive of an ACTH-independent Cushing's syndrome. And the value of more than 20 pg/ml is suggestive of ACTH-dependent Cushing's syndrome. Further testing is required if the values are equivocal. Patients with equivocal ACTH values between 10 and 20 pg/ml may be subjected to CRH stimulation test and the increment of the ACTH and cortisol response are suggestive of Cushing's disease.

High-dose dexamethasone suppression test (HDDST) though used to differentiate the pituitary from ectopic ACTH-dependent Cushing's syndrome is not commonly used now-a-days. The sensitivity and the specificity depend on the amount of cortisol suppression, and can be suppressed in carcinoid syndrome producing ACTH.

Other tests that are available to differentiate the cause of Cushing's syndrome are given below in **Table 4**.

Challenges and Limitations

- Adrenocorticotropic hormone values between 10 and 20 pg/ml are subjected to the CRH stimulation to differentiate, but the clinical clues like pigmentation and imaging has to be considered before coming to a conclusion. Although many tests are available, none of them clearly differentiate the patients with equivocal results. Therefore, lot of clinical discretion is required and the treating physician should also be aware of all the pitfalls of the diagnostic tests.
- Adrenocorticotropic hormone molecule is rapidly degraded by the plasma proteases. Hence, it should be collected in a prechilled ethylenediaminetetraacetic acid (EDTA) tube to avoid falsely low values. So while interpreting the value, ensure proper collection of the sample.
- High-dose dexamethasone suppression test shows suppression by only less than 50% of the basal cortisol value in about 80% of the patients with Cushing's disease. And there are high numbers of false positive tests (10-30%) in ectopic Cushing's syndrome.

IMAGING IN CUSHING'S SYNDROME

Once the diagnosis of ACTH or non-ACTH-dependent Cushing's syndrome is made appropriate imaging is done. In non-ACTH-dependent Cushing's CT/MRI of the adrenal gland is done but CT gives the better resolution of the adrenal anatomy.

In ACTH-dependent Cushing's syndrome, the first step is to image the pituitary and see if there is any abnormality and for this MRI of the pituitary is done with gadolinium enhancement. Use of dynamic MRI (with IV gadolinium) with spoiled gradient sequences increases the sensitivity of detection. But caution has to be exercised in diagnosing microadenomas as the possibility of an incidentaloma is as high as 10% in general population.

If the pituitary imaging is negative, then imaging of the head and neck, thorax and abdomen has to be done to detect the ectopic source of production of the ACTH [mostly thymoma, carcinoid, pheochromocytoma, medullary thyroid carcinoma (MTC) or malignancy]. In patients with suspected ectopic ACTH and not localized, special imaging like In-pentetreotide scintigraphy/^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is done.

Bilateral Inferior Petrosal Sinus Sampling

This is done in conditions where you have an ACTH-dependent Cushing's syndrome and the pituitary imaging is normal or having a lesion less than 6 mm. This is also used to lateralize the microadenoma within the pituitary. A basal central, peripheral ratio of 2:1 or a CRH-stimulated ratio of more than 3:1, is indicative of the Cushing's disease.

TABLE 4 | Tests to diagnose cause of Cushing's syndrome

Test	Method	Value	Sensitivity	Specificity	
CRH test	1 µg of ovine or human CRH	ACTH > 35% Cortisol > 20%	93% (for ACTH)	100% (for cortisol)	Used to diagnose Cushing's disease
HDDST	2 mg for 48 hours	> 90% suppression of basal 8:00 AM cortisol	67–70%	100%	Not much used now—unreliable
BIPSS	Petrosal sinus sampling	Basal central: Peripheral 2:1 CRH stimulated > 3:1	95%	100%	Used to differentiate pituitary and ectopic

Abbreviation: CRH, Corticotropin releasing hormone; HDDST, High-dose dexamethasone suppression test; BIPSS, Bilateral inferior petrosal sinus sampling

TABLE 5 | Medical therapy of Cushing's syndrome

Inhibit steroidogenesis	Metyrapone Ketoconazole	Days to weeks	Cause GI side effects and ketoconazole cause insufficiency
Inhibits glucocorticoid receptor	Mifepristone Etomidate	Days	Etomidate can be used for acute control
Modulate ACTH release	Cabergoline Octreotide SOM-320 Pasireotide	Months	Effect may be variable and slow
Adrenolytic	Op'DDD (Mitotane)	Days to weeks	Effect may be permanent

Challenges and Limitations

- Given the high incidence of both pituitary and adrenal incidentalomas imaging should be done only after confirming the hypercortisolism and ACTH values.
- Specially in ACTH-dependent Cushing's syndrome, if the pituitary shows a microadenoma restraint has to be exercised as it could be an incidentaloma and be interpreted along with the other tests like HDDST, CRH test and bilateral inferior petrosal sinus sampling (BIPSS).
- Bilateral inferior petrosal sinus sampling though projected as an ideal test to differentiate requires expertise to do the test and to catheterize into the veins.
- The clinical clues to differentiate ectopic from the Cushing's disease are male sex, atypical presentation, fast progression, very high cortisol/ACTH values and severe hypokalemia.

MANAGEMENT OF CUSHING'S SYNDROME

Non-ACTH-Dependent Cushing's Syndrome

Adrenalectomy is the treatment of choice for the ACTH-independent Cushing's syndrome. It can be either unilateral as in adenoma or malignancy or bilateral in case of bilateral hyperplasia. Management of this condition is adrenalectomy. Bilateral adrenalectomy remains an option for ACTH-dependent Cushing's syndrome not cured by other techniques and patients who are sick. But it carries the risk of developing Nelson syndrome and the life-time supplementation of gluco- and mineralocorticoids.

ACTH-Dependent Cushing's Syndrome

Surgical Management

Trans-sphenoidal surgery (TSS) remains the treatment of choice for the Cushing's disease and the remission rate depends upon the size of the tumor (macro/microadenoma), invasion of the tumor to the dura or cavernous sinus, histology and the expertise of the neurosurgeon. Microadenomas have a higher remission rate as high as 90% and less for the macroadenomas. Postoperative hypocortisolemia [< 50 nmol/L (1.8 µg/dL) at 9:00 AM] is probably the best indicator of the likelihood of long-term remission. And these patients should be started on steroid repalcement. Postoperatively, assessment for deficiencies of other pituitary hormones should also be sought, and the appropriate replacement regimen initiated as necessary. Patients who did not achieve remission can be given the option of a repeat TSS or radiation therapy or the medical therapy depending upon the patient's condition and the individual's choice.

If the ectopic ACTH-secreting tumor is benign and amenable to surgical excision, such as in a lobectomy for a bronchial carcinoid tumor, the chance of cure of Cushing's syndrome is high. However, if significant metastatic disease is present, surgery is not curative although it may still be of benefit in selected cases. In this situation, bilateral adrenalectomy may be an option if medical management fails.

Medical Management

Following are the indications for medical management in Cushing's syndrome **(Table 5)**:

- Preoperatively to control cortisol levels
- Patients in whom surgery is contraindicated
- Patients in whom surgery/radiotherapy is failed.

Metyrapone and ketoconazole are the ones who have rapid onset of action. Ketoconazole has been used in long-term treatment, with the dose ranging from 200 to 1,200 mg per day. Mitotane is an adrenolytic with lasting action on the adrenal and mostly these may develop hypocortisolemia.

Challenges and Limitations

- Though surgery offers the best option of cure for Cushing's disease, especially microadenoma, the chance of recurrence is as high as 25% over 4 years. Hence, these patients should be on regular monitoring. Also failed surgery rate is higher if the adenoma cannot be located and total or partial hypophysectomy carries a high-risk of hypopituitarism.
- It remains a challenge for the surgeon; since, postoperatively many will develop hormonal deficiencies including diabetes insipidus.
- Bilateral adrenalectomy performed in bilateral adrenal nodular hyperplasia and for failed TSS, need careful follow-up with steroid replacement. If done in ACTH-dependent Cushing's syndrome, imaging and ACTH have to be monitored because of the risk of developing Nelson's syndrome.
- Medical management remains an option where lesion is not localized and these patients need to be followed by imaging every 6 months to a year. Ketoconazole and mitotane treatment can cause hypocortisolemia and hence need to be monitored.
- Patients who did not have remission with the surgery should be offered other modalities of treatment, as untreated hypercortisolemia has high mortality and morbidity.

CONCLUSION

There has been a reappraisal of our understanding of Cushing's syndrome both in its diagnosis and management. The importance of diagnosing these cases early by looking for a few specific clinical pointers, and then screening them by judicious selection of one or more diagnostic tests is being realized. Referral of suspected cases to Specialist Centers with expertise and equipment to confirm or negate this suspicion should be the norm. These centers with their expertise and skill in the surgical techniques, medical and radiation intervention to target the culprit lesion, produce better remission and lesser recurrence. If such confirmation is not possible as indicated by

equivocal test results, one would be advised to repeat them after 6 months.

It is to be stressed that the test employed, whether hormonal or imaging don't have 100% sensitivity or specificity. Also it is worth remembering that Cushing's syndrome, whatever the cause, is a slowly evolving problem taking years to manifest with some of them passing through phases of eucortisolism. One should therefore not rush through in instituting therapeutic procedures.

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