Cushing’s syndrome: Stepwise approach to diagnosis

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ABSTRACT

The projected prevalence of Cushing’s syndrome (CS) inclusive of subclinical cases in the adult population ranges from 0.2–2% and it may no longer be considered as an orphan disease (2–3 cases/million/year). The recognition of CS by physicians is important for early diagnosis and treatment. Late-night salivary cortisol, dexamethasone suppression test, or 24-h urine free cortisol are good screening tests. Positively screened cases need stepwise evaluation by an endocrinologist. This paper discusses the importance of screening for CS and suggests a stepwise diagnostic approach to a case of suspected hypercortisolism.

Key words: Cushing’s syndrome, dexamethasone suppression tests, hypercortisolism, salivary cortisol, urinary free cortisol

INTRODUCTION

Cushing’s syndrome (CS) is a conglomeration of signs and symptoms resulting from sustained pathological hypercortisolism. On the one hand, diagnosis of CS is often missed initially owing to its rarity and overlapping characteristics with common disorders like metabolic syndrome. It is generally recognized later in its full-blown state. Classical cases typically have a history of symptoms for 1–2 years before the confirmation of diagnosis. Timely diagnosis and treatment of CS is important to decrease morbidity and mortality. To increase awareness about CS amongst patients and physicians alike, United States has declared April 8, 2007 as the National CS Awareness Day. In 2008, The Endocrine Society published clinical practice guidelines for diagnosis and treatment of CS.[1] In this clinical review, a stepwise approach for diagnosis of hypercortisolism is discussed so as to minimize both missing and misdiagnosing CS.

Undoubtedly, diagnosis of CS is often missed and delayed for the common metabolic syndrome variants. But the opposite is also true where over diagnosis of this condition can mislead us. In this clinical review, a stepwise approach for diagnosis of hypercortisolism is discussed so as to minimize both missing and misdiagnosing CS.

Step 1: Clinical suspicion and screening for hypercortisolism

There is no rule more invariable than that we are paid for our suspicions by finding what we suspect.

Henry David Thoreau

The normal hypothalamic-pituitary-adrenal (HPA) axis exhibits a circadian rhythm. Clinical manifestations of hypercortisolism are the result of an altered rhythm (quality) and excess cortisol load (quantum). Hypercortisolism has a broad spectrum of manifestations.[2] Overt CS is easily recognizable, but it is difficult to delineate subclinical CS from the patients attending obesity, diabetes, and hypertension outpatient clinics. Findings like visceral obesity, glucose intolerance, hypertension, and menstrual irregularities though common in CS are nondiscriminatory. Specific manifestations of hypercortisolism are those affecting skin (livid striae and ecchymoses), muscle (proximal myopathy) and bone (short stature in an obese child, vertebral compression fractures).[3] These catabolic manifestations are subtle in the early course of the disease and manifest with long standing and/or intense...
primary hypercortisolism. Hypertrichosis over the forehead is a useful clinical clue. Table 1 summarizes clinical features of CS.

Clinical intuition backed with an analytical approach is required to establish or exclude a diagnosis of subclinical CS.[3] The Endocrine Society guidelines recommend screening under the following circumstances:

1. patients with multiple, progressive, and discriminatory findings suggestive of CS
2. cases with unusual features like hypertension or osteoporosis at a young age
3. adrenal incidentalomas
4. children with a decreasing height percentile and increasing weight

Subclinical CS is seen in 5–30% cases of adrenal incidentalomas, which in turn are found in 4–7% of the adult population. Extrapolating this data, the prevalence of subclinical CS in adults would be 0.2–2.0%. CS is one of the differential diagnosis of polycystic ovarian syndrome, which is actually a diagnosis of exclusion.[4] Screening every diabetic patient for CS is not recommended even though the prevalence of occult CS ranges from 1–10% in various series.[5] This is because screening in this group is often associated with very high false positivity. In a study of 171 obese diabetic patients, 31 had unsuppressed overnight dexamethasone suppression cortisol. On follow-up testing, only three of them had elevated 24-h urinary free cortisol, two of whom were shown to have alcoholic pseudo-CS. Finally, there was only one true CS out of 31 patients with unsuppressed overnight dexamethasone suppression cortisol.[7] In such situations where clinical discrimination is poor, the pretest probability of CS in a diabetic individual equals the prevalence of this disorder in a diabetic cohort. With such a poor pretest probability even with the use of specific tests having good likelihood ratio, the posttest probability falls below 20%, which does not make us wiser.[9] Based on this statistical knowledge, routine screening in patients with individual components of metabolic syndrome is not advised at present.

**Step 2: Establishing endogenous hypercortisolism**

When you have mastered numbers, you will in fact no longer be reading numbers, any more than you read words when reading books. You will be reading meanings.

W. E. B. Du Bois

Before proceeding to the hormonal tests, history of exogenous glucocorticoid intake is imperative to rule out exogenous CS.[8] In India, cases of exogenous CS are commonly encountered, secondary to the ingestion of powdered/injectable medications for pains and aches dispensed indiscriminately. Some features such as increased intraocular pressure, cataracts, benign intracranial hypertension, aseptic necrosis of femoral head, osteoporosis, and pancreatitis are commoner in iatrogenic than in endogenous CS. The diagnosis is obvious, though can be confirmed by drug analysis and suppressed basal serum cortisol and plasma adrenocorticotropic hormone (ACTH).

History of depression, severe obesity, or chronic alcoholism may suggest pseudo-CS, i.e., reversible HPA axis hyperactivity. Usually such cases are clinically mild, may show suppressed cortisol with dexamethasone suppression test, and reverse to normal with treatment of an associated condition. The insulin tolerance test or loperamide test are rarely indicated.[9]

The test available for the quantitative estimation of cortisol load is 24-h urinary free cortisol. To assess the circadian rhythm and quality of the HPA axis, midnight serum cortisol and late night salivary cortisol tests are useful. The supressibility of the HPA axis is judged by the overnight dexamethasone suppression test (ODS), standard 2-day low-dose dexamethasone suppression test (LDDS), and LDDS–corticotrophin-releasing hormone (CRH) stimulation test. The methodology of these tests is briefly mentioned in Table 2.[1,10,13] Initial evaluation requires the determination of either UFC, late night salivary cortisol, ODS, or LDDS. In patients with a high index of clinical suspicion and an equivocal, discordant or negative initial test result, the subsequent evaluation of either midnight serum cortisol level or LDDS–CRH stimulation test is required. A schematic diagram for diagnosing a patient suspected of having CS is shown in Figure 1. The rationale behind such an approach is that initial tests have a high degree of sensitivity to rule

| Table 1: Clinical features of Cushing’s syndrome |
| Symptoms and signs | Proportion (%) |
| Obesity or weight gain | 95 |
| Facial plethora | 90 |
| Rounded face | 90 |
| Decreased libido | 90 |
| Thin skin | 85 |
| Decrease linear growth in children | 70–80 |
| Menstrual irregularity | 80 |
| Hypertension | 75 |
| Hirsutism | 75 |
| Depression/emotional lability | 70 |
| Easy bruising | 65 |
| Glucose intolerance | 60 |
| Weakness | 60 |
| Osteopenia or fracture | 50 |
| Nephrolithiasis | 50 |
In a patient with classical features of CS all tests perform well. The job of an endocrinologist is to delineate subclinical CS from the cohort of metabolic syndrome cases. The specificities of various tests to exclude CS in a cohort of an obese population are reported to be 96% for UFC, 90% for ODST and 92% for salivary cortisol.

The test results seem good; however, in actual sense, for an uncommon disorder like CS even a specificity of up to 99% may not be discriminatory. The following example elucidates this concept. In a cohort of 1000 obese people, consider that there is one case of CS. Even when a test with 99% specificity is applied, there would be 11 persons who would test positive (10 false positive + 1 true positive) for CS. Moreover, it is not easy to delineate the CS case from false positive ones even for the experts. So when the pretest probability is low, in order to increase the likelihood ratio, the endocrinologist must read the same test at higher cut-offs and analyze the results of multiple tests together.

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After excluding the exogenous CS, CD is the most common cause of endogenous hypercortisolism. Other causes are mentioned in Table 3.

### Adrenocorticotropic hormone dependency versus independency

Basal plasma ACTH with a two-site immunometric assay is a useful parameter for the diagnosis of adrenal CS. Patients with suppressed morning plasma ACTH (<5 pg/ml) need adrenal imaging. Normal or elevated ACTH (>15 pg/ml) is suggestive of ACTH-dependent CS. Plasma ACTH values between 5 and 15 pg/ml are equivocal.[9] In our series of CS patients, midnight plasma ACTH value of >7.5 pg/ml was suggestive of CD.[14] Even with an autonomous cortisol secreting adrenal adenoma, plasma ACTH levels may not be completely suppressed. Differentiation may not be easy as unilateral or bilateral adrenal enlargement is frequent in patients with an ACTH hypersecretion. Baseline CRH stimulation test can help to delineate the source in equivocal cases. Plasma ACTH peak levels of <30 pg/ml after corticotrophin releasing hormone CRH stimulation test excludes the presence of an ACTH-dependent hypercortisolism.[17]

### Adrenocorticotropic hormone-dependent cases: CD versus ectopic CS

A clinical setting provides important clues towards differential diagnosis. Females with, moderate hypercortisolism, mildly elevated plasma ACTH and normokalemia point towards CD. In contrast, males presenting with severe hypercortisolism, markedly elevated plasma ACTH and hypokalemia are more likely to have an occult ectopic ACTH-secreting tumor.[14]

In case of ACTH-dependent endogenous hypercortisolism, the pretest probability for pituitary origin is >80% overall and >90% in women.[14] Hence magnetic resonance imaging (MRI) of the pituitary region is the next step. There is emerging data that the spoiled gradient-recalled acquisition technique is superior to the conventional dynamic contrast spin echo.[18] The reported rate of visualization of pituitary microadenomas on MRI ranges from 50% to 70%. If the results of IPSS are negative or equivocal, further tests are required.

### Adrenocorticotropic hormone independent CS: Different etiologies

A CT scan of the adrenal gland can phenotype the adrenal lesion as benign (adenoma) and malignant (carcinomas) depending on the lipid content and contrast wash-out characters. Primary pigmented nodular adrenal disease (PPNAD) and McCune–Albright syndrome are unique causes of childhood CS. The classical paradoxical rise in cortisol after LDDS test is a feature of PPNAD.[23,24] ACTH independent macronodular adrenal hyperplasia (AIMAH) is a rare familial disorder, in which adrenal steroidogenesis is driven by non-ACTH peptides like vasopressin, glucose-dependent intestinal peptides, catecholamines, luteinizing hormone, etc. A specific test protocol has been described to recognize the stimulating peptide.[24] It is interesting to note that the identification of aberrant adrenal hormone receptors in AIMAH provides opportunities for new specific pharmacological therapies as alternatives to adrenalectomy.

### Table 3: Various causes of hypercortisolism

| ACTH dependent | ACTH independent |
|----------------|-------------------|
| Cushing's disease (70) | Adrenal adenoma (10) |
| Ectopic ACTH syndrome (10) | Adrenal carcinoma (5) |
| Ectopic CRH-secreting tumor | Primary pigmented nodular adrenal disease |
| | McCune–Albright syndrome |
| | ACTH independent macronodular adrenal hyperplasia (AIMAH) |

Numbers in parentheses denote % prevalence (not mentioned for rare etiologies)
**CONCLUSION**

Conducting a battery of tests for a clinically florid CS case to prove endogenous hypercortisolism is easy. Real difficulty arises while dealing with the subtle cases, where even the experienced endocrinologists have a tough time interpreting the test results and may resort to the wait-and-watch policy. The basic dictum which still serves as a golden rule is not to proceed further until there is convincing evidence of biochemical hypercortisolism.

While localizing the source, suppressed levels of plasma ACTH and positive adrenal imaging pave an easy path. In case of ACTH-dependent CS, an MRI scan report of clearly defined pituitary adenoma is rewarding. Equivocal or negative findings on an MRI scan mandates CRH-stimulated IPSS. Anyone who has encountered a good number of cases would have regretted his or her decision (at least once), by reliance on the pretest probability of it being pituitary without an IPSS. Localizing an ectopic tumor source is a herculean task.

Finally, efforts to fine-tune our approach to the more difficult aspects of CS must not eclipse with efforts to educate and encourage guided screening for patients who might benefit from evaluation.

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