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Cushing's Syndrome: Update on signs, symptoms and biochemical screening

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Abstract

Endogenous pathologic hypercortisolism, or Cushing's syndrome, is associated with poor quality of life, morbidity and increased mortality. Early diagnosis may mitigate against this natural history of the disorder.

The clinical presentation of Cushing's syndrome varies, in part related to the extent and duration of cortisol excess. When hypercortisolism is severe, its signs and symptoms are unmistakable. However, most of the signs and symptoms of Cushing's syndrome are common in the general population (e.g. hypertension and weight gain) and not all are present in every patient.

In addition to classical features of glucocorticoid excess, such as proximal muscle weakness and wide purple striae, patients may present with the associated co-morbidities that are caused by hypercortisolism. These include cardiovascular disease, thromboembolic disease, psychiatric and cognitive deficits, and infections. As a result, internists and generalists must consider Cushing's syndrome as a cause, and endocrinologists should search for and treat these co-morbidities.

Recommended tests to screen for Cushing's syndrome include 1 mg dexamethasone suppression, urine free cortisol and late night salivary cortisol. These may be slightly elevated in patients with physiologic hypercortisolism, which should be excluded, along with exogenous glucocorticoid use. Each screening test has caveats and the choice of tests should be individualized based on each patient's characteristics and lifestyle.

The objective of this review was to update the readership on the clinical and biochemical features of Cushing's syndrome that are useful when evaluating patients for this diagnosis.

Keywords

Cushing's syndrome; screening tests; symptoms

Signs and symptoms of Cushing's syndrome

Cushing's syndrome is caused by chronic exposure to excess cortisol. Its associated comorbidities contribute to decreased quality of life (1) and an increased standardized

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mortality rate compared to the general population (2–4). Although some studies show increased mortality regardless of remission status (4), most studies indicate that early diagnosis is important to reduce mortality and morbidity (6,7). Detection relies first on clinical suspicion, and then on biochemical confirmation.

The clinical presentation of Cushing's syndrome varies, in part related to the extent and duration of cortisol excess. When hypercortisolism is severe, its signs and symptoms are unmistakable. In particular, proximal muscle weakness, wasting of the extremities with increased fat in the abdomen, torso and face, and wide purple striae, suggest marked hypercortisolism. However, most of the signs and symptoms of Cushing's syndrome are common in the general population (Table 1), and not all are present in every patient. As a result, patients with mild or cyclic disease may not present in the more classical way. (Discussion of so-called "subclinical" Cushing's syndrome is beyond the scope of this article.)

Because of the variety in presentation, patients are often referred to subspecialists for complaints that are gynecologic (oligomenorrhea, hirsutism, infertility), dermatologic (red facial skin, poor wound healing, striae, acne), orthopedic/rheumatologic (fractures, low bone mineral density), metabolic (hypertension, diabetes, dyslipidemia), infectious (community acquired and infections seen with immunosuppression [8]), cardiovascular (stroke, myocardial infarction, pulmonary embolism [9]), neurologic (decreased strength, headaches, decreased memory and cognition), psychiatric (depression, anxiety, mood change) and non-specific (fatigue, backache and weight gain). Because of this, early detection may not occur unless the specialist considers other features not related to the referral question. It is important to screen for the associated comorbidities in patients with the disorder. Newer tests such as cardiac MRI (to study structure/function) and CT (to evaluate atherosclerosis) may be useful in the future but have not yet been validated fully (10,11). It is essential to treat co-morbidities, both while trying to establish the diagnosis, and beyond.

One might not suspect the diagnosis in milder cases based on a single visit without consideration of a complete history. However, Cushing's syndrome tends to progress over time, so that an accumulation of relevant features over time often leads to the diagnosis; previous photographs may help to identify this progression. One recent study showed that face classification software correctly classified nearly all patients (85%) and controls (95%) using facial photographs. Further prospective research in patients suspected of having Cushing's syndrome is needed to validate this tool (12).

A few recent studies compared the prevalence of various features in patients with established Cushing's syndrome, and those suspected to have the condition in whom it was excluded. The latter group is often referred to as having "pseudo-Cushing's syndrome" because they may have clinical features compatible with the syndrome, and sometimes biochemical features, but do not have endogenous pathologic hypercortisolism. In the first study, 32 patients with Cushing's syndrome were compared to 23 with pseudo-Cushing's syndrome (13). Easy bruising and osteoporosis were more common in patients with Cushing's syndrome but polycystic ovary syndrome was more common in those with pseudo-Cushing's syndrome. By contrast, the frequency of many features of Cushing's

syndrome were similar in both groups, including diabetes, hypertension, acne, hirsutism and menstrual disorders, probably reflecting the features that prompted evaluation.

In a second study, 53 of 73 patients were ultimately found to have Cushing's disease, while the remaining 20 were classified as having pseudo-Cushing's syndrome, despite having elevated urine free cortisol (UFC) and/or abnormal response to dexamethasone, 1 mg (14). Among the latter group, more than half had a BMI > 30 kg/m2 and moon facies or increased dorsocervical fat. Myopathy, hirsutism, acne and osteoporosis were present in less than 20%.

Mood and cognitive changes have long been recognized as important clues to the presence of Cushing's syndrome (15). Chief amongst these is the development of a more labile mood, with irritability and expressions of anger that may seem relatively unprovoked. Classically short-term memory is impaired, as is mental calculation—these can and should be evaluated at the bedside by history and recall of three objects and serial seven subtractions. Problems with sleep-onset and sleep-maintaining insomnia, as well as early morning awakening are common. General psychiatric functioning may deteriorate—often along the lines of the pre-morbid personality—e.g. the patient with occasional depression may develop a severe chronic depression when hypercortisolemic.

Biochemical Diagnosis of Cushing's Syndrome

While biochemical features of hypercortisolism may firmly establish the diagnosis, a variety of conditions are associated with mild physiologic hypercortisolism in the absence of Cushing's syndrome, as shown in Table 2. Cushing's syndrome may be suspected in these patients because of the presence of features that are common in the absence of Cushing's syndrome, such as weight gain, hypertension and mood changes. As noted above, such patients are often referred to as having "Pseudo-Cushing's syndrome" because they do not have the condition despite having mild hypercortisolism and compatible features. One approach to these patients is to wait to test until the condition has resolved (acute illness), is adequately treated (depression) or is abandoned (daily strenuous exercise), in which case the mild hypercortsiolism may resolve as well

The Endocrine Society's Clinical Practice Guideline for the diagnosis of Cushing's syndrome recommends that exogenous administration/ingestion of glucocorticoids be considered and excluded before performing screening tests. The guideline recommends using two of three screening tests to establish the diagnosis: UFC, late night salivary cortisol or 1mg dexamethasone suppression test (16). It is important to individualize the choice of test(s) and to perform more than one of the cortisol tests, if they are chosen, to minimize the effect of day-to-day variation.

A number of factors influence the outcome of screening tests for Cushing's syndrome. Common among them are the need for laboratory testing, and the requirement for accuracy and precision at low quantifiable hormone levels. These issues will be discussed in conjunction with each test.

Dexamethasone suppression test

The 1 mg overnight dexamethasone suppression test interrogates whether glucocorticoid negative feedback is normal. This outpatient test involves administration of dexamethasone, 1 mg by mouth, between 11pm and midnight, and measurement of serum cortisol between 8 and 9 AM the following morning. The results are normal if the cortisol is less than 1.8 ug/dl (50 nmol/L). (Higher values are associated with a lack of appropriate negative feedback in Cushing's syndrome patients.) This value is very close to the functional detection limit of some assays, so that inherent assay variability might account for an "abnormal" result close to the cut-off point.

Falsely abnormal results occur in a variety of settings. Women taking oral estrogens may have an increase in corticosteroid-binding globulin (CBG), which in turn increases total cortisol, potentially leading to abnormal results (17). Measurement of salivary cortisol was not found to be helpful in one study of 19 women on oral contraceptives; another study of 21 such women found improved specificity compared to use of serum cortisol as an endpoint (91 vs 62%). However, each of these was worse than the corresponding specificity of healthy control individuals not taking oral contraceptives (98% for each) (18). Thus, salivary cortisol after dexamethasone may be a better outcome measure than serum cortisol. However, its performance has not been compared to that of other screening tests in women taking oral estrogens.

Medications may accelerate or impair dexamethasone metabolism (19) potentially causing falsely normal or abnormal results, respectively (20). Dexamethasone is metabolized by the CYP3A4 complex, which is stimulated or inhibited by many commonly used drugs. Valassi et al studied whether medication use altered the results of the test (21). They found that those patients who did not have Cushing's syndrome but were taking medications were more likely to have an abnormal test result that those who were medication-free (Specificity 70 vs. 96% respectively, $p = 0.014$). Conversely, in another study, up to 8% of patients with Cushing's disease had a normal response (i.e. suppression) to the low dose dexamethasone suppression test (22). Measurement of dexamethasone levels can help to identify potential abnormal clearance of dexamethasone, but has not come into general practice (23).

UFC

UFC reflects the integrated tissue exposure to free cortisol over 24 hours, and so provides a unique perspective on glucocorticoid physiology that is different from the other two tests. The choice of assay technique appears to affect whether a patient with mild Cushing's syndrome will have a normal or abnormal UFC (24,25). This is explained by cross-reactivity with cortisol precursors and metabolites in immunoassays, which is not present in the structurally-based assays such as high performance liquid chromatography or tandem mass spectrometry (26). As a result a patient may have a normal result in the structurally based assay but an abnormal result in the immunoassay. The pre-test probability (27) may influence the decision to use UFC—with a low pre-test probability suggesting this choice.

As mentioned earlier, the pseudo-Cushing states are associated with a physiologic increase in UFC—for such individuals, other screening tests may be preferable. Caveats to the test

include its inconvenience, with the attendant possibility of under or over-collection. For this reason, measurement of both creatinine and volume are helpful to assess completeness and patients must be able to comply with the correct collection procedures. UFC is falsely raised when the volume is greater than 5L (28) and falsely low when glomerular filtration rate falls (29).

More than one UFC measurement is needed to avoid false negative results, to detect cyclic hypercortisolism and to validate the diagnosis, as patients with Cushing's disease may have quite variable UFC (30), ranging from normal to severely elevated values in the same patient.

Salivary cortisol

Serum and salivary cortisol reach a nadir just after sleep initiation (31); this entrained circadian phenomenon is disrupted when sleep occurs at different times of the day such as with shift work or travel to a new time zone. Patients with Cushing's syndrome lose this diurnal nadir and have increased serum and salivary cortisol values at bedtime compared with obese and pseudo-Cushing's patients (24,32). Salivary cortisol has the advantage of allowing for in-home collection using a salivette (a cotton pledget in a plastic tube); since cortisol is thermally-stable at room temperature, the collection can be mailed to a laboratory for analysis. One caveats for salivary cortisol is that it increases with age, hypertension and diabetes (33), so that its use in such patients may give a falsely positive result. Additionally, immunoassays may increase the false positive rate (34), potentially because of cross-reactivity with cortisone, which salivary glands convert from cortisol via 11 beta hydroxysteroid dehydrogenase type 2 (35). A major advantage of salivary cortisol is that it tends to be abnormal when UFC (measured by structural assays) is normal or only mildly elevated in patients with proven Cushing's syndrome (8,20).

A Cushing's syndrome index

This idea was advanced by Nugent et al in 1964, who stated "In the differential diagnosis.. [of Cushing's syndrome], the physician uses clinical signs and simple laboratory data in addition to information …from past experiences to make a decision concerning the probability of the diagnosis…"(36). The authors developed a Bayesian equation using the incidence of signs and symptoms of Cushing's syndrome in 211 patients. They then used the equation to calculate the probability of Cushing's syndrome in 111 patients. The clinical features included osteoporosis, central/generalized obesity, weakness, bruising/acne, plethora, colored striae, edema, hirsutism, oligomenorrhea, headache, abnormal glucose tolerance, age < 35 years, diastolic blood pressure > 105 mm Hg, red blood cell volume > 49 fL, and serum potassium < 3.6 mEq/L. This approach returned a "confident" diagnosis of Cushing's syndrome in 9/38 patients with the disorder, and the exclusion of the syndrome in 45/93 without the disorder.

Unfortunately, the results of this Bayesian analysis do not give high positive (16%) and negative (61%) predictive values. However, the concept of an "index" deserves to be re-evaluated with current data.

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Table 1

Signs and symptoms of Cushing's syndrome

More Common	Less Common
Decreased libido	EKG abnormalities or atherosclerosis
Obesity /weight gain	Dorsal fat pad
Plethora	Edema
Round face	Abnormal glucose tolerance
Menstrual changes	Osteopenia or fracture
Hirsutism	Headache
Hypertension	Backache
Eccymoses	Recurrent infections
Lethargy, depression	Abdominal pain
Striae	Acne
Proximal muscle weakness	Female balding

Table 2

Physiologic hypercortisolism

Some clinical features of CS may be present
Pregnancy
Depression and other psychiatric conditions (32,33)
Alcohol dependence
Glucocorticoid resistance
Morbid obesity
Poorly controlled diabetes mellitus
Unlikely to have any clinical features of CS
Physical stress (hospitalization, surgery, pain) (34)
Malnutrition, anorexia nervosa
Intense chronic exercise
Hypothalamic amenorrhea
CBG excess (increased serum but not UFC)