

Screening For Cushing's Syndrome in Primary Care: Which Test is The Best?



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Abbreviations: UFC: Urinary Free Cortisol; DST: Dexamethasone Suppression; CBG: Cortisol Binding Globulin; RIA : Standard Cortisol Radioimmunoassay

Introduction

Cushing's syndrome (CS) is defined as an outcome of prolonged exposure to glucocorticoids whether from outside or inside sources. It's a relatively rare condition with an incidence of 0.7-2.4 per million population per year [1]. Clinical presentation in primary care setting can be highly variable, and establishing the diagnosis can often be difficult and is frequently missed due to its rarity and overlapping characteristics with common disorders like metabolic syndrome. Early diagnosis and treatment of CS is associated with a decrease in morbidity and mortality [2]. The objective of this article is to discuss the most appropriate screening test that could be performed in primary care in clinically suspected cases of CS.

Etiology of Cushing's Syndrome

Exogenous administration of glucocorticoids (Iatrogenic CS) is the most common cause of CS. Table 1 shows the various causes of endogenous CS. ACTH dependent CS accounts for 80-85% of cases, of which around 75-80% are due to pituitary adenoma. Chronic alcoholism, depression and severe obesity may lead to reversible hyperactivity of HPA axis and cause pseudo-CS [1,2].

Table 1: Causes of Endogenous CS [2] ACTH- Adrenocorticotropic hormone, CRH-Corticotrophic releasing hormone.

ACTH Dependent	ACTH Independent
Pituitary dependent CS (Cushing's disease)	Adrenal adenoma
Ectopic ACTH syndrome	Adrenal carcinoma
Ectopic CRH-secreting tumor	Primary pigmented nodular adrenal disease. McCune-Albright syndrome. Macronodular and Micronodular adrenal hyperplasia

Clinical Features of Cs

Table 2 discusses the various clinical features of CS. Certain features of the skin, muscles and bones are specific for CS that helps to differentiate it from simple obesity. Clinical features like cataract, raised intraocular pressure, aseptic necrosis of femoral head and osteoporosis are more common in iatrogenic CS [1].

Table 2: Clinical Feature of CS [12] DVT: Deep vein thrombosis.

Specific Features	General Features
Body - Abnormal fat deposition leading to Weight gain, obesity, moon face, buffalo hump.	Cardiovascular system - Hypertension, hypokalemia, edema, atherosclerosis.
	Metabolism - Diabetes mellitus/glucose intolerance, dyslipidemia,
Skin - Purple striae, facial plethora, thin and brittle skin, easy bruising, acne, hirsutism.	Reproductive system -Decreased libido, menstrual irregularities in women mainly amenorrhea due to reduced gonadotrophin secretion due to effect of cortisol
Bone - Osteopenia, osteoporosis, mainly involving the vertebrae leading to reduced linear growth.	Central nervous system - Irritability, depression, cognitive defects, paranoid psychosis.
Muscle - Weakness and proximal myopathy	Blood and immune system - Hypercoagulation with risk of DVT or pulmonary embolism and susceptibility to infections.

Whom to Screen

Although CS is relatively rare, studies of patients with diabetes, obesity, hypertension, and osteoporosis found a high prevalence of CS among these populations [3]. The Endocrine Society guidelines recommend screening under the following circumstances: [4]

- Patients with multiple, progressive, and discriminatory findings suggestive of CS.
- Cases with unusual features like hypertension or osteoporosis at a young age
- Children with a decreasing height percentile and increasing weight
- Adrenal incidentalomas
- Patients with familial disease that puts them at risk of CS.
- It recommends against widespread testing for CS other than the above patient group.

Screening Tests for Cushing’s Syndrome in Primary Care Settings (Table 3)

Table 3: Screening Tests for CS [2] UFC- Urinary free cortisol, OCP- Oral contraceptive pills.

Test	Method	Cut-off value	Remarks
24hr UFC	Two samples to be collected and refrigerated	>300ug/day Sensitivity- 90% Specificity- 96%	False Positive: Excess water intake, drugs like carbamazepine False Negative: Renal impairment
Late Night Salivary Cortisol	Two samples between 11 pm and 12 am	>145ng/ml Sensitivity >90% Specificity 92%	False Positive: oral licorice, tobacco, altered day, night cycle, stress
Overnight Dexamethasone suppression test (DST)	Oral dexamethasone (1mg) at 11pm and serum cortisol 8 am, next morning	>1.8ug/dl Sensitivity >90% Specificity 80%	False positive: drugs like phenytoin, pregnancy, OCP. Test can be affected by variability in absorption and metabolism of dexamethasone
Low dose DST	Oral dexamethasone 0.5mg 6hrly for 2 days, serum cortisol level 6 hrs after the last dose	>1.8Ug/dl	

It is recommended by the Endocrine Society guidelines [4] that one of the following tests be performed for screening of CS:

1. 24hr Urinary free cortisol (UFC) (at least two measurements)
2. Late-night salivary cortisol (two measurements)
3. 1-mg overnight Dexamethasone Suppression Test (DST)

4. Longer low-dose DST (2mg/d for 48h)

24hr UFC

24 hr UFC looks at the unbound cortisol secretion that is filtered by the kidneys over a 24hr period and is not affected by conditions and medications that alter Cortisol Binding Globulin (CBG). Normal values: <90 microgram/24hours (250nmol/day). Values more than 300microgram/day (830nmol/day) are considered diagnostic. Sensitivity of this test in detecting cortisol excess is 95%, specificity is 98%. False positive and false negative results may occur (Table 3). UFC should be confirmed with repeat testing [5].

Late night salivary cortisol

Physiological cortisol secretion follows a circadian rhythm. Serum cortisol concentration reaches its peak in the morning (0600–0800h) and is lowest in the night during the first half of normal sleep. Normal circadian rhythm of cortisol secretion is lost in patients with CS. Salivary cortisol is measured at 23:00 hours and 07:00 hours using a standard cortisol radioimmunoassay (RIA). The upper limit of reference range is 145ng/dl (3.6nmol/L) and sensitivity is >92%. LNSF is a simple and reliable screening test for spontaneous Cushing’s Syndrome and useful for screening large, high risk population (patients with diabetes mellitus) [4].

Dexamethasone suppression test (DST)

In standard DST patient is given 1mg dexamethasone orally at 11pm and the plasma cortisol level is measured at 8 am next morning. In the 48-h low dose DST test, dexamethasone is given at the dose of 0.5 mg every 6 h for 2 days at 090h, 1500h, 2100h, and 0300h with measurements of cortisol in serum 6 hours after the last dose of dexamethasone (normal<1.8ug/dl). The sensitivity of this test is 98%; specificity is 80%. Normal findings in both the test make CS unlikely. Obesity, chronic illness, chronic alcoholism and depression can cause false positive results (pseudo-Cushing syndrome) [5].

Discussion

Cushing’s syndrome is a relatively rare condition [6], and can present to primary care in many different ways, making the diagnosis a challenging one to reach. It is an important diagnosis to consider, as it has a significant impact upon morbidity and mortality, and early detection and treatment can have a significant impact on improving life expectancy [7]. Unfortunately, however, it is a diagnosis that is frequently ‘missed’, with a mean time to diagnosis of 6 years in one study [8].

In the primary care setting, the ideal first-line screening test would be very sensitive (ie. all those with Cushing’s syndrome would be detected, and none would be missed), practically possible in the community, acceptable to the patient and cost-effective [6].

Around the world all other tests except 24hr UFC, need to be performed in the hospital setting so the most readily available in the primary care setting is the 24hr UF [9]. 24hr UFC looks at the unbound cortisol secretion that is filtered by the kidneys over a 24hr period. This test is usually considered overall to have a high diagnostic sensitivity in adults and children, it is important to correlate test results with creatinine ratios to ensure a complete collection [4]. This test also has multiple external factors that can cause or mask false negative/positive results such as excess fluid intake, certain medications and improper collections. It is vital to obtain a thorough assessment to take place to accurately access results. [3]. In the pediatric population, even with a high sensitivity of 89% it is still recommended to follow up the UFC with a second test mentioned above to confirm a diagnosis [10].

24 hour urinary free cortisol levels appears to be the most practical first-line test to perform in primary care in patients where there is a high probability of Cushing's Syndrome, because it is non-invasive and widely available [8]. However, in patients who have a lower probability of Cushing's syndrome, it may be advantageous to consider late night salivary cortisol or 1-mg overnight dexamethasone, because both of these tests are more sensitive, reducing the likelihood of false negative results [8]. Unfortunately, late night salivary cortisol is not a test that is widely available to primary care physicians in the UK [11]. The 1mg overnight dexamethasone suppression test is possible to organize in primary care, with a well motivated patient, but the practicalities of timing the administration of the drug and the blood test, make it slightly more of a challenge [12].

Conclusion

In summary, when screening for Cushing's syndrome in primary care in the UK, a 24hour urinary free cortisol level is a useful test for the majority of patients, particularly when they have symptoms that make the diagnosis of Cushing's Syndrome

likely. In a patient who is less likely to have Cushing's Syndrome, but needs screening to exclude the diagnosis, 1mg overnight dexamethasone testing may be preferable, due to the higher sensitivity of the test.

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