Evaluation of adrenocortical function in adults

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Summary

Cushing's syndrome is caused by increased concentrations of cortisol. Most cases can be detected by measuring the free cortisol in a urine sample collected over 24 hours. In Cushing's syndrome the increased secretion of cortisol is not reduced during a dexamethasone suppression test. Addison's disease is caused by a decreased secretion of cortisol that does not respond to an injection of synthetic adrenocorticotrophic hormone. Concentrations of adrenocorticotrophic hormone are raised in primary, and low or normal in secondary adrenal insufficiency. Some patients with hypertension have primary aldosteronism. They have a high ratio of aldosterone to plasma renin activity. When investigating adrenal function it is important to consider the patient's diet and drugs as well as the timing of the sample.

Key words: Addison's disease, aldosterone, Conn's syndrome, cortisol, Cushing's syndrome.

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Introduction

The adrenal cortex consists of three functionally separate layers. The outer zona glomerulosa produces aldosterone under the stimulatory control of the renin-angiotensin system and potassium. Aldosterone increases sodium reabsorption and potassium excretion in the kidney and gut. The zona fasciculata produces cortisol under the control of pituitary adrenocorticotrophic hormone (ACTH). ACTH is principally regulated by hypothalamic corticotrophin-releasing hormone. The secretion of ACTH responds to a diurnal rhythm, stress and negative feedback from circulating cortisol. Cortisol regulates metabolism, and during stress it restrains and redirects the immune system and accentuates cardiovascular responses. The inner zona reticularis produces the adrenal androgens dehydroepiandrosterone and androstenedione.

Clinical evaluation determines which tests of adrenal function are needed. The principles of testing include:

- using basal hormone concentrations for screening
- using suppression or stimulation tests to definitively diagnose hormone excess or deficiency
- measuring trophic hormones to diagnose the site of endocrine lesions (for example, measuring ACTH to distinguish an adrenal from a pituitary lesion in hypocortisolism).

Testing for hypercortisolism (Cushing's syndrome)

Mild Cushing's syndrome is notoriously difficult to diagnose, but early diagnosis avoids disability and reduces mortality. Cortisol concentrations increase in Cushing's syndrome, but there are two major confounders. One is that some patients have increased cortisol production rates that remain within the statistically normal range. Furthermore, this overproduction may be intermittent or cyclic. Secondly, some individuals may have transient hypercortisolism and features consistent with early Cushing's syndrome, but without the progressive catabolic effects. These individuals have 'pseudo-Cushing's'. In some cases this is associated with alcohol abuse or depression. No single test is infallible in Cushing's syndrome and values close to the limits of normal must be regarded with suspicion.[1]

Screening tests for Cushing's syndrome

Most cases can be readily diagnosed by an elevation of the free cortisol in a 24-hour collection of urine, however in up to 15% of new cases the result may be normal. The dexamethasone suppression test also has a substantial false positive and false negative rate. The diagnosis can be made with plasma cortisol, but the blood sample has to be taken at midnight and this is often impractical. A midnight value less than 120 nmol/L virtually excludes Cushing's syndrome.

Urinary free cortisol

Over 24 hours the free cortisol provides an integrated assessment of cortisol secretion. This avoids the pitfalls of blood tests including circadian rhythm, pulsatile cortisol release and altered levels of corticosteroid-binding globulin. However,

urine volumes above four litres per day may result in false positive tests.

Cortisol excretion rates vary diurnally but urine creatinine excretion does not. Hence, it is not possible to correct an incomplete or over-collection with the 24-hour urine creatinine. Urinary creatinine is useful in determining if the urine collection was adequate, for example a low 24-hour urine creatinine in a large person may suggest under-collection. In addition, in sequential measurements the 24-hour urine creatinine should not vary by more than 10%.

False positive results can occur in patients with high urine volumes, chronic alcoholism, depression, idiopathic pseudo-Cushing's, or serious illness. False negatives may occur in patients with early or mild Cushing's syndrome, or in those with cyclic hypercortisolism which occurs in 10% or more of cases depending on how cyclic is defined.

Midnight plasma cortisol

Cortisol peaks around the time of waking, decreases rapidly through the morning and reaches a nadir around midnight. Most patients with Cushing's syndrome have early morning plasma cortisol concentrations within or slightly above the normal range. In contrast, midnight plasma cortisol concentrations are almost always high (greater than 207 nmol/L).

Midnight salivary cortisol

Salivary cortisol concentrations reflect plasma free cortisol, but appropriate assay-specific normative values must be used for its interpretation. Internationally, cut-offs have ranged widely. We have found a cut-off of 13 nmol/L to reliably distinguish Cushing's from non-Cushing's patients.

Low-dose dexamethasone suppression testing

A low dose of dexamethasone should suppress plasma cortisol. This is commonly used as a screening test for Cushing's syndrome. Dexamethasone, 1 mg orally, is given at 11 pm and plasma cortisol is measured at 8–9 am the next day to see if it has been suppressed. The dexamethasone suppression test has been variously validated in the past, often with inappropriate controls, such as normal volunteers. Low cut-off values (50 nmol/L or less) tend to over-diagnose, while high cut-off values (140 nmol/L or above) tend to miss cases of Cushing's syndrome. False positive results can occur in acute illness, depression, anxiety, alcoholism, high oestrogen states and with drugs that accelerate dexamethasone metabolism. If a low dose does not suppress cortisol, a high-dose dexamethasone suppression test is indicated.

Testing for primary hypoadrenalism (Addison's disease) and ACTH deficiency

Hypoadrenalism may be caused by abnormalities in the adrenal gland or a lack of ACTH. Adrenal suppression is also an adverse effect of corticosteroids.

Although fatigue is a key symptom of hypoadrenalism, most fatigued people have normal adrenal function. There is no single cheap and convenient test for evaluating hypoadrenalism.[2] Testing includes an ACTH stimulation test, and measurements of sodium, potassium, ACTH, plasma cortisol, aldosterone and renin activity.

Plasma cortisol

An early morning plasma cortisol, measured within one hour of waking, below 200 nmol/L strongly suggests adrenal insufficiency. Conversely, a plasma cortisol greater than 500 nmol/L excludes the diagnosis and obviates the need for an ACTH stimulation test. Intermediate cortisol concentrations may require investigation with an ACTH stimulation test.

ACTH stimulation testing

In most cases of suspected hypoadrenalism, a stimulation test is needed to diagnose cortisol deficiency. A normal response to intravenous ACTH (250 microgram) is a cortisol peak value at either 30 or 60 minutes of greater than 500 nmol/L. The previously recommended additional criterion of a cortisol increment greater than 200 nmol/L rarely contributes to the diagnosis.

There are cases of missed adrenal insufficiency after a normal ACTH test. The reproducibility of testing is imperfect. The test has not been validated against clinical end points, but has been validated against the now rarely used insulin hypoglycaemia test.

Plasma ACTH

Measurement of plasma ACTH helps localise the cause of adrenal insufficiency – adrenal (primary or Addison's) versus pituitary (secondary) or hypothalamic (tertiary). In primary adrenal insufficiency, plasma ACTH is greatly elevated due to a lack of the negative feedback of cortisol on the hypothalamic-pituitary axis. In secondary or tertiary adrenal insufficiency, ACTH is low or inappropriately normal.

Corticotrophin-releasing hormone test

The use of corticotrophin-releasing hormone to test ACTH and cortisol reserve directly assesses pituitary and adrenal function. Other than minor flushing, corticotrophin-releasing hormone (1 microgram/kg intravenously) rarely produces adverse effects. The test is expensive and corticotrophin-releasing hormone is not widely available.

Testing for primary aldosteronism

Conn's syndrome is hypertension and hypokalaemia due to an aldosterone-secreting adrenal tumour, however many cases are normokalaemic. Screening for primary aldosteronism may be indicated in patients with hypertension who have spontaneous or thiazide-induced hypokalaemia.[3]

Plasma aldosterone concentration:plasma renin activity ratio

A mid-morning blood sample is taken from a seated patient. In primary aldosteronism, the plasma renin activity is reduced

and the plasma aldosterone concentrations are high, resulting in a plasma aldosterone concentration (pmol/L):plasma renin activity (ng/mL/hr) ratio of greater than 700. A false positive may occur with low aldosterone concentrations if the plasma renin activity is very low, for example in patients taking a high salt diet. Hence, an elevated ratio may not suggest primary aldosteronism if the plasma aldosterone concentration is less than 270 nmol/L.

Serum potassium should be measured simultaneously as a low serum potassium will reduce the plasma aldosterone concentration and indicate a requirement to replace potassium before testing again. Antihypertensive drugs, except for hydralazine, prazosin and verapamil, can also interfere with the plasma aldosterone concentration:plasma renin activity ratio. Diuretics and aldosterone receptor blockers such as spironolactone need to be stopped for six weeks before testing. Beta blockers suppress the plasma renin activity but they can be stopped for 24–48 hours before testing. The effects of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists are generally minor, but in a patient treated with these drugs a detectable plasma renin activity level or a low plasma aldosterone concentration:plasma renin activity ratio does not exclude the diagnosis of primary aldosteronism. Dihydropyridine calcium antagonists such as nifedipine and amlodipine can reduce the plasma aldosterone concentration in patients with an aldosterone secreting adenoma. Renal impairment may elevate the ratio as increased potassium elevates aldosterone secretion while salt and water retention suppresses the plasma renin activity.

Confirming primary hyperaldosteronism

Confirmatory testing aims to demonstrate aldosterone secretory autonomy, using measurements of plasma or urine aldosterone under salt loading conditions, with or without fludrocortisone. The final step is to determine if one or both adrenals are the source of aldosterone, generally requiring adrenal vein sampling.

Adrenal incidentaloma

An unanticipated adrenal mass (incidentaloma) is found in approximately 4% of upper abdominal computed CT scans. Clinical, imaging and biochemical evaluation is necessary to exclude malignancy and hormone excess.[4] The risk of adrenocortical cancer is very low, but adrenal metastases are common and need to be considered in patients with a history of cancer.

Conclusion

Disorders of adrenocortical function are uncommon and the symptoms often non-specific. Application of a small number of biochemical screening tests can separate those patients who do not have a disorder of adrenal function from those who require specialised assessment and more complex testing.

References

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 167)

1. Most patients with primary hyperaldosteronism have hyperkalaemia.
2. A normal 24-hour urine free cortisol excludes Cushing's syndrome.