

BLOOD SCIENCES
DEPARTMENT OF CLINICAL BIOCHEMISTRY

Title of Document: Investigation of Cushing's Syndrome
Q Pulse Reference N^o: BS/CB/DCB/EN/11
Authoriser: Michelle Young

Version N^o: 7

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INVESTIGATION OF CUSHING'S SYNDROME

Introduction

Cushing's syndrome is a collective name for a number of endocrine conditions associated with the overproduction of cortisol by the adrenal gland. Cortisol production is controlled by the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary and is under negative feedback control from cortisol. Excess cortisol production can be secondary to an ACTH secreting pituitary tumour (Cushing's disease, 70% of cases), ectopic secretion of ACTH (12% of cases) or an adrenal adenoma/carcinoma (18% of cases).

Indications

Testing for Cushing's syndrome in adults, after excluding exogenous glucocorticoid use, is recommended with:

- Multiple and progressive features compatible with the syndrome, particularly those with a high discriminatory value (e.g. facial plethora, easy bruising, striae, and proximal myopathy)
- Unusual features for age (e.g. osteoporosis, hypertension, and type 2 diabetes);
- Adrenal incidentaloma

First line screening tests

Random cortisol is not an effective screening tool

Those that may be used are:

1. Overnight dexamethasone suppression test (see BS/CB/DCB/EN/10)
2. At least two 24 hour urinary free cortisol (in a plain 24 hour urine bottle)
3. A paired midnight and waking salivary cortisol

In general, these tests have equal accuracy in detecting Cushing's syndrome but 24 hour urine free cortisol can be increased by high fluid intake, stress and medications, whilst midnight salivary cortisol may be affected in shift workers, depression and the critically unwell. There are also difficulties with collecting saliva and 24 hour urine so the local policy is to recommend an overnight dexamethasone suppression test which is more appropriate in morbid obesity, depression, alcohol excess and diabetes.

There are some special circumstances that apply:

- Pregnancy – Advise 24 hour urinary cortisol
- Women on the combined contraceptive should ideally stop 6 weeks prior to dexamethasone suppression test or use 24 hour urinary free cortisol.
- Enzyme inducing medication, e.g. anticonvulsants, can increase dexamethasone clearance therefore 24 hour urinary cortisol advised.

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- Chronic kidney disease- dexamethasone suppression test should be used rather than 24h hour urinary cortisol.
- Adrenal Incidentaloma – Either dexamethasone suppression test or salivary cortisol should be used.
- Urine and salivary cortisol should be used in suspected cyclic Cushing's syndrome

Second line investigation

The endocrinologist has to choose second-line tests:

1. Either one or two of the above
2. Low dose dexamethasone test (+/- CRH)
3. High dose dexamethasone suppression test.
4. ACTH (EDTA sample, to reach lab within 10 minutes and on ICE)

Principle of the tests

Low dose dexamethasone Suppression test (LDDST)

- 1) 9 a.m cortisol (serum) and basal ACTH (EDTA) prior to the test on day 1.
- 2) 0.5 mg dexamethasone 6 hourly for 48 hrs, (09.00, 15.00, 21.00, 03.00 both days)
- 3) 9 a.m cortisol (serum) at the end of the test on day 3 (6 hrs after last Dexamethasone dosage)

Failure to suppress cortisol to <50nmol/L suggests the diagnosis of **Cushing's Syndrome**. False positives can still occur, however there are fewer false positives compared to the overnight dexamethasone suppression test.

Yanovski test, using ovine CRH

Similar to low dose dexamethasone test; it is used to try and differentiate pseudo-Cushing's syndrome from true Cushing's syndrome.

There is controversy regarding its specificity. Note that usually ovine CRH is used in the USA, and human CRH is used in Europe. The cut-off currently applied to the test derives from work carried out with ovine CRH and cannot be automatically superimposed for those employing human CRH. European Endocrine guidelines suggest that it is not as specific as LDDST but is included here as it is occasionally used.

- 1) Start at 12:00hrs and take basal cortisol(serum) and ACTH (EDTA).
- 2) Give 0.5mg dexamethasone at 12:00, 18:00, 24:00 and 06:00 hrs for both days.
- 3) Cortisol at 08:00 on third day – 2 hours after last dose.
- 4) IV 100mcg CRH at 08:00 then cortisol at 15, 30, 45 and 60 minutes afterwards.

Cushing's syndrome is excluded by suppression of cortisol <50nmol/l after the LDDST and cortisol <38nmol/l 15 minutes after CRH

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High dose dexamethasone suppression test (HDDST)

- 2mg Dexamethasone 6 hourly for 48 hours
- Differentiates Cushing's disease from ectopic ACTH production.
- In pituitary ACTH driven bilateral adrenal hyperplasia (**Cushing's Disease**), a suppression to greater than 50% the original value occurs.
- In ectopic ACTH and adrenal adenoma cases suppression of cortisol with higher dose dexamethasone usually does not occur.

ACTH measurements

- ACTH levels are suppressed in adrenal adenoma, raised (usually above reference range) in ectopic production and normal to slightly raised in pituitary driven disease.
- All results must be interpreted in the light of simultaneous cortisol levels. Isolated, random ACTH levels are pointless.

References

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