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Sub-Clinical Cushing's Syndrome: A Critical Analysis

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SUBCLINICAL CUSHING'S SYNDROME (SCC)

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- The name of the syndrome is problematic
- Adrenal adenoma with autonomous cortisol secretion in absence of overt symptoms of Cushing syndrome.
- Frequency: 5-20% of incidentalomas; variability related to diagnostic criteria, some estimates are much higher
- In overt Cushing's syndrome: clinical features a spectrum; depends on extent of hormone excess and variable phenotypic expression
- In SCC: phenotype is variable and not readily identifiable
- HPA abnormalities also a spectrum
  - Non-functional to subclinical
  - Subclinical to overt

Inconsistencies in Approach

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Subclinical Cushing's Syndrome

- Index of suspicion based on incidental radiology finding
- Standard screening test
- Leads to either repeated screening or additional testing (often normal)
- Criteria for disease can rest entirely on positive screening test
- Equivocal results are common and treatment seems to be more strongly suggested

Cushing's Syndrome

- Index of suspicion based on signs and symptoms of disease
- Series of tests to increase or decrease the probability of disease
- Diagnosis is challenging and fraught with false positives and negatives, rests on an accumulation of evidence

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Pituitary Incidentaloma

- Index of suspicion based on clinical evaluation of comorbidities
- Screening follows guidelines for evaluation of Cushing's syndrome
- Choice of screening test with abnormal results followed by one or two additional tests for abnormal cortisol secretion
- Equivocal results usually warrant observation

Variations in Diagnostic Testing

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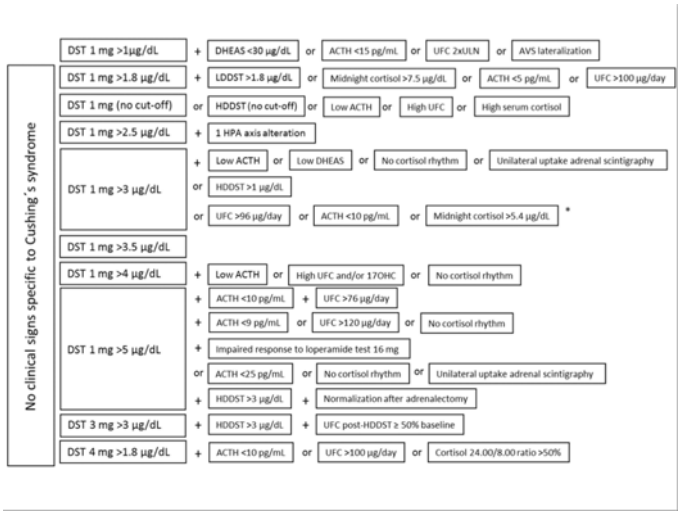

Di Dalmazi J Clin Endocrinol Metab, August 2014, 99(8):2637–2645

Diagnosing Subclinical Cushing's Syndrome (SCS)

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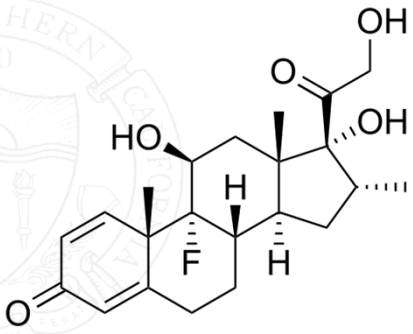
- Test of autonomous hypercortisolism
  - 1 mg overnight dexamethasone
    - Cut points
      - <1.8µg/dl sensitivity 95%, specificity 70-80%
      - <5µg/dl increases false negatives, specificity 95%
  - Morning ACTH/DHEAS levels
    - Indirect assessment of adrenal autonomy
  - Adrenal scintigraphy – measurement of activity of nodule, and contralateral gland
- Tests of hypercortisolism
  - 24-hour UFC – Less sensitive to detect mild hypercortisolism
- Tests of Diurnal rhythm
  - Late night serum cortisol
  - Late night salivary cortisol (two samples)
- No clear separation of normal from abnormal cortisol secretion
  - No test is adequate in sensitivity to completely rule out cortisol excess 100% of the time
  - No test has the specificity to identify patients with true disease 100% of the time

Dexamethasone Suppression

- Commonly recommended initial screening test
  - Convenient
  - Rapid results
  - 1mg overnight dexamethasone suppression test
    - Assessment of corticotroph negative feedback by glucocorticoid suppression of ACTH secretion
    - No direct effect on adrenal secretion of cortisol
    - 16 methyl modification of the D ring of the dexamethasone molecule allows for lack of cross reactivity with assays of endogenous cortisol and metabolites

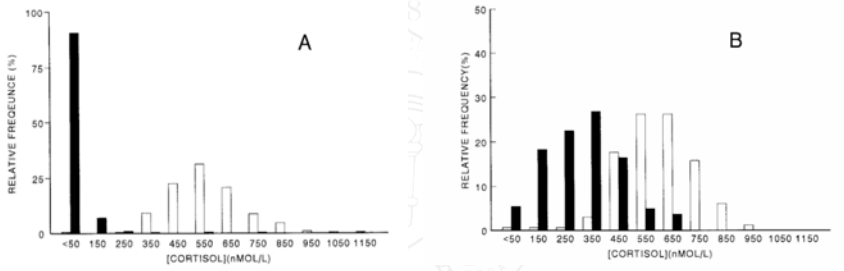


Dexamethasone Testing: Sources for Error

- Usual culprits for false positives: obesity, depression, alcohol withdrawal (pseudo-Cushing's states)
- Relies on measurement of serum cortisol
  - Cortisol binding globulin may influence results
    - Exogenous estrogens
    - CBG levels vary between and within individuals[1]
- Variation in dexamethasone metabolism
  - Drugs or foods that alter hepatic CYP3A4 activity
    - Barbiturates, phenytoin, rifampin, carbamazepine
- Anorexia/hypocaloric diet
- Intense exercise
- Glucocorticoid receptor polymorphisms
  - ER22/23EK and 9β polymorphisms
    - Associated with decreased glucocorticoid sensitivity and relative resistance
    - Occur in 2.5% and 16.5% (heterozygous carriers 5% and 28%), respectively[2]

1 Dhilo, et al. European Journal of Endocrinology 146 231–235 (2002)
2 Quax, R. A. *et al. Nat. Rev. Endocrinol.* 9, 670–686 (2013)

Variation in Response to Dex



Huizenga *J Clin Endocrinol Metab* **83:** 47–54, 1998

Importance of the Cutoff Point

- Initial development of the test:
  - Normal response < 5mcg/dl (140 nmol/L)[1]
- Current, more specific immunoassays
  - Most normal subjects suppress to < 2mcg/dl (55nmol/L)[2]
- A cutoff of 1.8 mcg/dl maximizes sensitivity, decreases specificity
  - Few false negatives
  - Higher number of false positives

1 Meikle AW, et al J Alab Clin Med 1975
2 Blethen SL Steroids 1989

Effect of Raising the Cutoff Point

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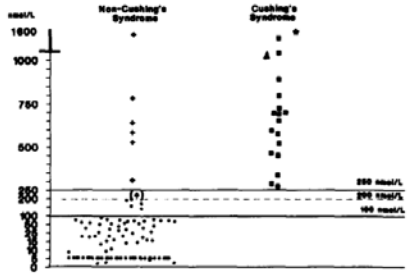
- Raising the cutoff point would increase specificity at the cost of sensitivity
- Reduces False Positives/Increases True Negatives
- Also Increases False negatives/Reduces true positives



Montwill et al. *Steroids* 59: 296-298, 1994.

Additional Tests

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- Repeat of Dex Suppression testing (varying dose or cutoff point)
- ACTH
- DHEA-S

- Not usually recommended:
  - 24h UFC – not sensitive enough to detect mild hypercortisolism
  - Salivary cortisol has been equivocal
  - High dose or 2 day low dose dexamethasone tests

No Consensus on Criteria

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- Diagnosis of SCS is entirely based on biochemistry (with adrenal adenoma)
  - No consistent methods to diagnose patients
  - No phenotype that is consistently linked to abnormal biochemistry that is not highly prevalent in the general population
  - No predictable progression to overt disease that could help define patients with "pre-clinical" disease

Approaches Toward Management

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Conservative Follow up

- Natural history of incidentaloma unknown
- Annual unenhanced CT for 2 years (? Continue imaging at 2 year intervals for tumors 2-4cm)
- Annual 1mg dexamethasone suppression testing for 3-4 years. If cortisol levels progressively rise, perform confirmatory tests (UFC, midnight salivary cortisol)

Surgical Treatment

- Tumor size and radiographic phenotype
  - 4-6 cm, concerning features – resect
  - 4cm, benign phenotype – resect if <40 years of age + comorbidities
- Consider resection if recent onset or worsening of disorders attributable to hypercortisolism (osteoporosis, hypertension, diabetes mellitus)
- Perioperative glucocorticoid supplementation required