Pearls and pitfalls in the management of Cushing’s Syndrome

AACE Annual Meeting, Austin, TX
May 5, 2017
Cushing’s Syndrome

- A symptom complex that reflects excessive tissue exposure to cortisol
- The diagnosis requires both clinical and biochemical signs of hypercortisolism
- Without treatment, increased mortality & morbidity
- Etiology-specific tumor resection allows HPA axis recovery
Overview

Diagnosis of CS
- Salivary cortisol
- UFC
- Dexamethasone suppression

Differential Diagnosis of CS
- ACTH levels
- Is MRI = MRI true?
- IPSS
  - false negative results
  - false positive results
- Localizing an Ectopic ACTH–producing tumor

Treatment
- Transsphenoidal surgery
- Using steroidogenesis inhibitors
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Cushing’s syndrome suspected

Exclude exogenous glucocorticoid exposure

Perform one of the following tests

- 24-h UFC (> 2 tests)
- Overnight 1-mg DST
- Late night salivary cortisol (> 2 tests)

Consider caveats for each test
Use 48-h, 2-mg DST in certain populations

ANY ABNORMAL RESULT

Normal (CS unlikely)

Exclude physiologic causes of hypercortisolism

Consult endocrinologist

Perform 1 or 2 other studies shown above
Suggest consider or repeating the abnormal study
Suggest Dex-CRH or midnight serum cortisol in certain populations

Discrepant
(additional evaluation)

ABNORMAL
Cushing’s syndrome

Normal (CS unlikely)

Nieman L et al. JCEM 93:1526, 2008
Late Night Salivary Cortisol

Cortisol (ug/dL)

CLOCK TIME (HOURS)
Late-night Salivary Cortisol

#1 Excitement can elevate LNSC

- Can nonspecific excitement or anxiety could influence LNSC?
- 15 HVs were studied at 2300 h and 0700 h after watching a Sunday evening Green Bay Packers football game (1900–2200 h).
- Despite a reported high level of excitement, only one subject had an abnormal 2300-h salivary cortisol, of 22.8 nmol/L.
LNSC in older, diabetic, hypertensive male veterans

#2 Confounders may lead to abnormal LNSC

UFC for the diagnosis of Cushing’s Syndrome

#3 Cyclic CS may give normal UFC results
Cyclic CS occurs at all ages, all etiologies
May be associated with variable s/s
Regular or irregular periodicity (4 d – years)
Regular or irregular duration (1 d – months)
1 mg Overnight Dexamethasone Suppression Test

- Morning cortisol < 1.8 ug/dL as screening cut-off
- Very close to assay detection
- Up to 30% false positive rate
- 5% false negative rate in CD
Effect of Medications on Post-LDDST cortisol

<table>
<thead>
<tr>
<th>Cut-off 1.4 ug/dL (38nmol)</th>
<th>Meds</th>
<th>No Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity % (95% CI)</td>
<td>73.3 (64.7–81.9)</td>
<td>85.7 (78.9–92.5)</td>
</tr>
<tr>
<td>Specificity % (95% CI)</td>
<td>70 (59–81)</td>
<td>96.1 (92.4–99.9) p = 0.014</td>
</tr>
</tbody>
</table>

Valassi E et al. J Clin Endocrinol Metab 94:4851-9, 2009
#4 Drugs may interfere with DST results

**Drugs that induce CYP 3A4 and accelerate dexamethasone metabolism**
- Phenobarbital
- Primidone
- Ethosuximide
- Phenytin
- Carbamazepine
- Rifampin
- Rifapentine
- Pioglitazone

**Drugs that inhibit CYP 3A4 and impair dexamethasone metabolism**
- Aprepitant/fosaprepitant
- Itraconazole
- Ritonavir
- Fluoxetine
- Diltiazem
- Cimetidine

**Drugs that increase CBG and may falsely elevate serum cortisol**
- Estrogens
- Mitotane

**Drugs that increase UFC results (may depend on assay)**
- Carbamazepine
- Fenofibrate
- Some synthetic glucocorticoids (immunoassays)

**Drugs that inhibit 11β-HSD2 (licorice, carbenoxolone)**

[http://medicine.iupui.edu/flockhart/table.htm](http://medicine.iupui.edu/flockhart/table.htm)
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The adrenal axis in Cushing’s Syndrome

- **Cushing Disease**
  - CRH → ACTH → Cortisol
- **Ectopic ACTH Secretion**
  - CRH → ACTH → Cortisol
- **Primary Adrenal Disease**
  - CRH → ACTH → Cortisol
Basal ACTH

#5 ACTH levels overlap among the causes of CS
Differential diagnosis of Cushing’s syndrome

Measure ACTH

Normal or high: ACTH dependent
- Pituitary MRI
  - IPSS
    - Cushing’s disease
      - Treat
    - Ectopic ACTH
      - Image for lesion

And/or
- 8 mg Dex and CRH

Undetectable or normal: ACTH independent
- Image adrenal glands for unilateral vs bilateral lesion
- Surgery
Imaging for corticotrope tumors

- Only about half of CD patients have tumors on conventional T1-weighted SE MRI imaging
- Retrospective analysis of 18 of 84 consecutive patients with surgically-proven CD
  -- each had a falsely-negative MRI at the referral institution and a positive MRI at NIH
- Comparison of technical MRI parameters
MRI results

• MRI interscan interval was 5.4 +/- 1.1 months

• Technical similarities
  ✷ All scans used Gad, had similar matrix sizes and most had 3-mm thick slices

• Technical differences
  ✷ Shorter repetition time [TR] 400 vs 492 +/- 19 ms, P = 0.0002
  ✷ Shorter echo time [TE] 10.3 +/- 0.5 vs. 17.2 +/- 1.2 ms, P = 0.0003
  ✷ Smaller FOV 12 x 12 cm vs. 17 +/- 0.6 x 18 +/- 0.7 cm, P < 0.0001
Outside vs NIH MRI

MRI technique, especially FOV and TR/TE influences results

#6 Not all Pituitary MRIs are the same

Chowdhury IN et al. Clin Endocrinol (Oxf) 72:502,2010
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Inferior Petrosal Sinus Sampling (IPSS)

Catheterize petrosal sinuses and peripheral vein
Bilateral and simultaneous sampling
Use of CRH (FDA: peripheral test)
Samples: Two Basal, 2, 5, 10 min post-CRH
Measure ACTH
Criteria: Central-to-peripheral ACTH > 2 before or > 3 after CRH
Any positive response = CD
About 95% sensitivity and specificity
False negative IPSS

4/501 patients with surgically-proven CD had false-negative IPSS.

Each had hypoplastic or plexiform IPS ipsilateral to an ACTH-secreting tumor.

Of 100 control patients,

- 75% had large, bilaterally symmetrical IPSs.
- 18% had asymmetrical IPSs; 11 L, 7 R
- 7% had bilaterally small petrosal sinuses.
- Of the 25% with unilateral or bilateral atrophic sinuses, none had false-negative sampling results.

#7 Review the venogram if IPSS does not show C:P gradient

Doppman JL et al. J Clin Endocrinol Metab 84:533, 1999
IPSS interpretation

Cyclic CS

~5 weeks before admission had sustained hypercortisolism (UFC > 1000 ug/d)
IPSS (UFC 27 ug/d; 3 d later 755; ref < 45)
CD based on CRH response and C:P IPSS ratio

<table>
<thead>
<tr>
<th>min</th>
<th>R</th>
<th>L</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>25.5</td>
<td>25.1</td>
<td>18.3</td>
</tr>
<tr>
<td>0</td>
<td>24.5</td>
<td>26.8</td>
<td>18.7</td>
</tr>
<tr>
<td>2</td>
<td>68.3</td>
<td>106</td>
<td>19.5</td>
</tr>
<tr>
<td>5</td>
<td>128</td>
<td>212</td>
<td>22.4</td>
</tr>
<tr>
<td>10</td>
<td>115</td>
<td>161</td>
<td>33.8</td>
</tr>
</tbody>
</table>

Chest CT/MRI --> mass
Hypocortisolemic after resection of carcinoid

#8 Beware IPSS with insufficient suppression
Results IPSS

- Inferior petrosal sinus to peripheral (IPS:P) gradients indicated CD in 491/501 patients (98%)
- All 10 pts with false negative IPSS had peak petrosal sinus ACTH concentrations <400 pg/ml (~90 pmol/L)

#9 Beware IPSS with petrosal sinus ACTH < 400 pg/ml
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  Localizing an Ectopic ACTH–producing tumor

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Diagnoses in 90 NIH patients; 48 female

Localization of an ectopic ACTH-secreting tumor

Imaging

CT and MRI of chest (abdomen, neck)
Octreotide as adjunctive imaging (~66% sensitivity)
F-DOPA PET (FDG offers little additional information beyond CT/MRI)

Biochemical Markers

Plasma metanephrines, calcitonin, 5-HIAAA
# Imaging Results

<table>
<thead>
<tr>
<th>ACTH-secreting carcinoid</th>
<th>n</th>
<th>Chest CT (+)</th>
<th>Chest MRI (+)</th>
<th>Abd. CT (+)</th>
<th>Abd MRI (+)</th>
<th>SRS (+)</th>
<th>Image correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>35</td>
<td>27/35</td>
<td>23/27</td>
<td>2/31</td>
<td>1/25</td>
<td>9/12</td>
<td>35/35</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1</td>
<td>0 / 0</td>
<td>0 / 0</td>
<td>0 / 0</td>
<td>1 / 1</td>
<td>0 / 1</td>
<td>1 / 1</td>
</tr>
<tr>
<td>NET</td>
<td>13</td>
<td>4 / 12</td>
<td>4 / 10</td>
<td>5 / 13</td>
<td>4 / 11</td>
<td>6 / 10</td>
<td>13 / 13</td>
</tr>
</tbody>
</table>

Zemskova MS et al. J Clin Endocrinol Metab 95:1207, 2010
ACTH-producing NET may be small

#10 Get thin cuts and look closely to detect tumor

Thymic NET

Pulmonary carcinoid

Zemskova MS et al. J Clin Endocrinol Metab 95:1207,2010
Ectopic ACTH secretion imaging summary

No single imaging modality can identify and localize every tumor responsible for EAS.

Any single imaging study may represent a false-positive result.

Use all imaging studies together.

Identification of tumors:
- Most within 6 months
- Repeated work-up as for as long as 12 yr
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In 28 studies published from 2001 to 2010, remission rates ranged from 51–97% and recurrence rates ranged from 2–27%.
#11 Surgical technique affects results

Incising pituitary capsule to identify capsule of tumor at its interface with normal gland

Dissection at interface of tumor capsule and pituitary

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"You have an extremely, rare, hard-to-treat disease — are you trying to make me look bad?"
Agents That Inhibit Steroidogenesis

Ketoconazole/etomidate
Metyrapone
Aminoglutethimide
Mitotane
Trilostane
Ketoconazole Treatment

No long-term data as monotherapy in CD
400 – 1,600 mg/day; every 6–8 hours
Gastric acid metabolizes it to active drug
Case

64-year-old female with Cushing’s disease, hypopituitarism s/p XRT

Previous Rx mitotane, cyproheptadine, ketoconazole: all ineffective

No new pituitary target
Taking Zantac

Still hypercortisolemic up to 2x normal
Referred to exclude ectopic ACTH secretion and consider treatment
Evaluation shows C:P ACTH step up with IPSS, positive response to CRH, no suppression with dexamethasone; empty sella
Central hypothyroidism, hypogonadism, low IGF-I

What is the diagnosis, and what is the best treatment?
Stop Zantac, start ketoconazole

#12 Ensure gastric acidity when using ketoconazole

The graph shows the changes in pCortisol and UFC levels over 14 days. The use of ketoconazole and dexamethasone is indicated with shaded areas. The graph helps to visualize the impact of these medications on hormone levels.
"I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least part of the work."

Letter to Dr Henry Christian
Nov 20, 1911
Thank you
NiemanL@nih.gov