MILD HYPERCORTISOLISM DUE TO ADRENAL ADENOMA: IS IT REALLY “SUBCLINICAL”? 

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Disclosures

• none
Case

• 68 yo F with adrenal mass noted on CT-urogram
• Dedicated CT showed 3.0 cm left adrenal mass with HU of -3 c/w benign adrenal adenoma
• PMHx: HTN, hyperlipidemia, osteopenia with vertebral FX and impaired glucose tolerance
• ROS: weight gain of 25 lbs in 18 months
Imaging
Case

Mild hypercortisolism due to adrenal adenoma

? Further workup or treatment?

- Laboratory w/u:
  - PM cortisol 6.5 mcg/dl, ACTH <10
  - DHEA-S = 31 mcg/dl (low)
  - Midnight salivary cortisols: 1.4 nmol/L and 1.6 nmol/dl (nl)
    - 1 mg dex suppression - cortisol 6.1 mcg/dl
  - 24-hr UFC 55mcg/24 hr and 49 mcg/24 hr (upper limit 45)
  - Aldosterone 7.0 ng/dl, PRA 0.4
  - Serum catecholamine levels normal
Emotional disturbance
Enlarged sella turcica
Moon facies
Osteoporosis
Cardiac hypertrophy (hypertension)
Buffalo hump
Obesity
Adrenal tumor or hyperplasia
Thin, wrinkled skin
Abdominal striae
Amenorrhea
Muscle weakness
Purpura
Skin ulcers (poor wound healing)
Cushing Syndrome

- Excess glucocorticoids cause Cushing Syndrome – may be exogenous or endogenous

**Screening Tests**
- 24 hour urine for urinary free cortisol
- Midnight salivary cortisols
- 1 mg overnight dexamethasone suppression test with measurement of AM serum cortisol, ACTH and dexamethasone levels
  - **Not useful in women on OCPs**
Table 6–8. Classification and etiology of Cushing’s syndrome.¹

<table>
<thead>
<tr>
<th>ACTH-dependent</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing’s disease</td>
<td>68</td>
</tr>
<tr>
<td>Ectopic ACTH syndrome</td>
<td>15</td>
</tr>
</tbody>
</table>

ACTH-independent

| Adrenal adenoma                         | 9       |
| Adrenal carcinoma                       | 8       |

| Total                                    | 100     |
Adrenal Cushing

- Epidemiology
- Biochemical Diagnosis
- Sequelae
- Treatment Options
Adrenal Incidentaloma

- Any serendipitously identified mass of >1 cm in the adrenal glands
- Autopsy studies suggest the rate of clinical unapparent nodules identified at death to be 6%
- Incidence increases with age
- Most are non-secreting and benign adenomas
Incidentaloma and the Beatles

‘EMI scanner’ (aka CT scan): 1972

Developed by Sir Godfrey Newbold Hounsfield in Britain at Electric and Musical Industries (EMI) Central Research Laboratories
Brain scans only
Required a water-filled, pre-shaped rubber "head-cap"
First appeared in the scientific literature in 1970’s

First publication discussing adrenal “incidentalomas”

19% of patients had an incidentally found adrenal lesion “Unsuspected primary and metastatic neoplasms of the adrenals were occasionally detected in patients scanned for other reasons. CT seems to be a simple and accurate method to assess the adrenal glands in patients suspected of adrenal disease.”
Adrenal Incidentaloma

Age:
- <30 years of age: 0.2%
- >70 years of age: 6.9%

Overwhelming majority are benign (particularly if <3 cm)
Adrenal Incidentaloma

Hormonal Activity

Young WF, *NEJM*, 2007

- Cortisol
- Phaeochromocytoma
- Aldosterone
- ACC
- Non-Secreting

4-5%
Adrenal Incidentaloma

Hormonal Activity

30% Cortisol

Risk Factors for Adrenal Cushing

• Bilateral Tumors
• Tumors larger than 2.4 cm diameter
• Somatic mutations in the catalytic subunit of protein kinase A (PRKACA)
  • present in 1/3 of adenomas associated with overt Cushing
Adrenal Cushing

Subclinical Cushing?
Adrenal Cushing

- Epidemiology
- Biochemical Diagnosis
- Sequelae
- Treatment Options
Subclinical Cushing Laboratory Definitions

- Abnormal DST
- May or may not have altered circadian rhythms
- UFC is often normal or nearly normal
- ACTH may not be suppressed
### Laboratory Definitions

**TABLE 2. Accuracy of HPA axis secretion parameters in diagnosing SH**

<table>
<thead>
<tr>
<th>First author, year (Ref.)</th>
<th>No. of patients</th>
<th>CCR (SN/SP)</th>
<th>ACTH (SN/SP)</th>
<th>UFC (SN/SP)</th>
<th>DST (SN/SP)</th>
<th>DEX dose, DST cutoff</th>
<th>Gold standard criteria for SH diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantero, 2000 (9)</td>
<td>1004</td>
<td>43/83</td>
<td>79/85</td>
<td>76/88</td>
<td>73/90</td>
<td>1 mg, 5 μg/dl</td>
<td>≥2 out of CRH, CCR, ACTH, UFC, DST</td>
</tr>
<tr>
<td>Libè 2002 (52)</td>
<td>64</td>
<td>n.a.</td>
<td>41/96</td>
<td>33/96</td>
<td>91/98</td>
<td>1 mg, 5 μg/dl</td>
<td>≥2 out of CRH, CCR, ACTH, UFC, DST</td>
</tr>
<tr>
<td>Masserini, 2009 (32)</td>
<td>103</td>
<td>22.7/87.7</td>
<td>86.4/59.3</td>
<td>31.8/92.6</td>
<td>86.4/96.3</td>
<td>1 mg, 3 μg/dl</td>
<td>≥2 out of DST, ACTH, UFC</td>
</tr>
<tr>
<td>Nunes, 2009 (31)</td>
<td>48</td>
<td>77/69&lt;sup&gt;a&lt;/sup&gt;</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>1 mg, 2.2 μg/dl</td>
<td>DST plus ACTH or CCR</td>
</tr>
<tr>
<td>Barzon, 2001 (67)</td>
<td>83</td>
<td>n.a.</td>
<td>n.a.</td>
<td>44/100</td>
<td>75/72</td>
<td>1 mg, 5 μg/dl</td>
<td>Norcholesterol scintigraphy</td>
</tr>
<tr>
<td>Valli, 2001 (48)</td>
<td>31</td>
<td>n.a.</td>
<td>n.a.</td>
<td>58/83</td>
<td>63/75</td>
<td>1 mg, 5 μg/dl</td>
<td>Norcholesterol scintigraphy</td>
</tr>
<tr>
<td>Eller-Vainicher, 2009 (58)</td>
<td>60</td>
<td>64.1/81&lt;sup&gt;d&lt;/sup&gt;</td>
<td>64.1/38</td>
<td>48.7/81</td>
<td>33.3/85.7</td>
<td>1 mg, 5 μg/dl</td>
<td>Postsurgical hypocortisolism</td>
</tr>
<tr>
<td>Morelli, 2010 (59)</td>
<td>231</td>
<td>n.a.</td>
<td>52.4/60.5</td>
<td>42.9/80</td>
<td>59/52.4</td>
<td>1 mg, 3 μg/dl</td>
<td>Postsurgical hypocortisolism</td>
</tr>
<tr>
<td>Eller-Vainicher 2010 (60)</td>
<td>55</td>
<td>65.2/65.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n.a.</td>
<td>n.a.</td>
<td>91.3/56.3</td>
<td>1 mg, 2.0 μg/dl</td>
<td>Metabolic improvement after surgery&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CRH, Blunted response to CRH; CCR, altered circadian cortisol rhythm (elevated MSeC or MSeC levels); ACTH, low ACTH levels [<10 pg/ml (2.2 pmol/liter)]; UFC, 24-h UFC levels above the upper limit of the normal range; DST, reduced cortisol suppression after a DST; DEX, dexamethasone; n.a., data not available; SN, sensitivity (%); SP, specificity (%).

<sup>a</sup> MSeC levels [cutoff, 1.7 μg/liter (47 nmol/liter)].

<sup>b</sup> MSeC levels [cutoff, 4.9 μg/dl (135 nmol/liter)].

<sup>c</sup> MSeC [cutoff, 4.0 μg/dl (110 nmol/liter)].

<sup>d</sup> MSeC [cutoff, 5.4 μg/dl (149 nmol/liter)].

<sup>e</sup> Concomitant presence of vertebral fractures, arterial hypertension, and type 2 diabetes mellitus.

<sup>f</sup> Improvement after surgery of at least two out of the following possible complications of SH: blood pressure, fasting glucose, body weight, and cholesterol levels.

Chiodini I, *J Clin Endocrinol Metab*, 2011
1mg Overnight Dexamethasone Suppression Test

- AM Cortisol
  - >1.8 ug/dL: 75-100%
  - > 5 ug/dL: 44-58%

Sensitivity: 75-100% (for >1.8 ug/dL), 44-58% (for > 5 ug/dL)
Specificity: 67-72% (for >1.8 ug/dL), 83-100% (for > 5 ug/dL)

*Chiodini, I. "Diagnosis and Treatment of Subclinical Hypercortisolism." JCEM, May 2011, 96(5): 1223-1236.
Adrenal Cushing

- Epidemiology
- Biochemical Diagnosis
- Sequelae
- Treatment Options
Subclinical Cushing

- Adverse effects on Bone
  - Chiodini et al., 2016, Eur. J Endo: BMD decrease spine, vertebral FX 46-82%

- Hypertension

- Insulin resistance/Impaired glucose metabolism/body composition/NFLD
  - Ivovic et al. Metabolism 2013
  - Androulakis et al, JCEM 2014
  - DeBono M et al, JCEM 2013 (visceral fat accumulation)

- Duration of cortisol exposure is associated with increase risk for morbidity and mortality
  - Lambert J et. al. (E. Geer) JCEM 2013

- Increased cardiovascular risk
Hypercortisolism and CV Mortality

- Androulakis et al, JCEM 2014 – Patients with apparently non-functioning AI at increased CV risk due to increased cortisol secretion. 60 pts with AI vs 32 Controls. Further stratified 60 AI into 26 CSAI (> 3mcg/dl post Dex), 34 NFAI. CSAI worse than NFAI worse than C.
198 patients - 114 stable non-secretory, 61 stable with intermediate or SCC, 23 had worsening pattern.

Average followup 7.5 years (range 26 mos. To 15 yrs)

Figure 2: Kaplan-Meier curves showing all-cause and cardiovascular-specific mortality

Dalmazi GD et al, Lancet, 2014
CVEs in AI: Morelli et al. JCEM 99:827-834, 2014

- 206 AI pts >5 yr followup
- SH = 1 mg dex with cortisol > 5mcg/dl or at least 2: low ACTH, high UFC, 1mg dex cortisol > 3 mcg/dl
- 24 pts with SH initially, 15 more developed over time (8.2%) (some with dex suppression > 1.8 mcg/dl initially). SH+ and SH- many grew and noted bilateral adenomas.
- SH patients – more diabetes and CVEs and larger adenomas. Cutoff size >2.4 cm
- CVEs correlate with dex suppressed cortisol between 1.5 and 2.0 mcg/dl (best SN and SP)
What’s in a Name?

• Any disease that has these sequelae is not “subclinical”
• “Subclinical” suggests that treatment is not necessary

“Mild Hypercortisolism”
Back to our case… 3cm adrenal incidentaloma in patient with metabolic syndrome and vertebral fracture

- NOT PRIMARY ALDOSTERONISM
- NOT PHEOCHROMOCYTOMA
- 24 hour urinary free cortisol mildly elevated, overnight dex suppression cortisol only suppressed to 6.1, low DHEAS and low ACTH
- Mild Hypercortisolism
Adrenal Cushing

• Epidemiology
• Biochemical Diagnosis
• Sequelae
• Treatment Options
Systematic review of surgical treatment of subclinical Cushing syndrome.

Iacobone M et al. *Brit J Surgery March 2015*

- 105 papers screened; 7 selected
- Laparascopic surgery preferred
- Improvement in HTN, metabolic parameters
- However, heterogeneity (particular in definition of SCC) and low quality of data preclude definitive recommendations.
Adrenalectomy reduces the risk of vertebral FX in patients with AI and mild hypercortisolism. 


- 605 patients with unilateral adrenal incidentalomas
- 55/605 with mild hypercortisolism
- 32/55 had adrenalectomy, followup 2-3 years
- BMD increased in surgery group, less vertebral FX (30% risk reduction) than in the observation group
Innovations in the medical management of Cushing’s syndrome seem akin to London’s red buses—none come along for ages and then three arrive together, namely, mifepristone, pasireotide and LCI699.”

Peter Trainer (Manchester, UK, editorial JCEM April 2014, 99:1157-1160)
Adrenal Cushing

- Adrenal incidentalomas are increasingly common.
- As many as 30% may be producing small amounts of excess cortisol.
- “Subclinical Cushing” is not-so-subclinical.
- Even low levels of excess cortisol can contribute to obesity, metabolic syndrome, osteoporosis, cardiovascular morbidity and mortality.
- Treatment options include observation, surgery and new medical therapies.
Thank you

• Gillian Goddard
• Aarti Ravikumar
• Nandita Sinha
• Jose Sanchez Escobar

• Eliza Geer
• Alexander Kirschenbaum