Subclinical Cushing’s Syndrome

AACE 26th Annual Scientific & Clinical Congress
Associate Clinical Professor of Medicine and Clinical Chief
University of Miami Miller Scholl of Medicine
Miami, Florida
aayala2@miami.edu

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Objectives

- Review the concept of “Subclinical” Cushing’s Syndrome (SCS)

- Establish a diagnostic and therapeutic approach, consider biases

- Discuss future directions
Full-blow Cushing’s Syndrome (CS)

- UFC > 4 x normal
- Lack of dexamethasone suppression
- Loss of cortisol diurnal rhythm
<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased fatigue</td>
<td>100</td>
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<tr>
<td>Decreased libido</td>
<td>33-100</td>
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<tr>
<td>Weight gain</td>
<td>79-97</td>
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<tr>
<td>Irritability</td>
<td>40-86</td>
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<tr>
<td>Insomnia</td>
<td>69</td>
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<tr>
<td>Decreased concentration</td>
<td>66</td>
<td></td>
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<tr>
<td>Impaired short-term memory</td>
<td>83</td>
<td></td>
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<tr>
<td>Changes in appetite</td>
<td>54</td>
<td></td>
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<tr>
<td>Lethargy, depression</td>
<td>40-67</td>
<td></td>
</tr>
<tr>
<td>Menstrual changes</td>
<td>35-86</td>
<td>49</td>
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<tr>
<td>Osteopenia</td>
<td>48-83</td>
<td>94</td>
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<tr>
<td>Headache</td>
<td>47-58</td>
<td>63</td>
</tr>
<tr>
<td>Backache</td>
<td>39-83</td>
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</table>

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Sens</th>
<th>Spec</th>
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<tbody>
<tr>
<td>Glucose intolerance</td>
<td></td>
<td></td>
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<tr>
<td>Difficult to control HTN</td>
<td></td>
<td></td>
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<tr>
<td>Recurrent infections</td>
<td>14-25</td>
<td></td>
</tr>
<tr>
<td>Plethora</td>
<td>78-94</td>
<td>69</td>
</tr>
<tr>
<td>Round Face</td>
<td>88-92</td>
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<tr>
<td>Hirsutism</td>
<td>64-84</td>
<td>61</td>
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<tr>
<td>Hypertension</td>
<td>74-90</td>
<td>83</td>
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<tr>
<td>Eccymoses</td>
<td>60-68</td>
<td>94</td>
</tr>
<tr>
<td>Striae wider than 1 cm and purple in color</td>
<td>50-64</td>
<td>78</td>
</tr>
<tr>
<td>Weakness</td>
<td>56-90</td>
<td>93</td>
</tr>
<tr>
<td>Abnormal fat distribution</td>
<td>34-67</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>48-66</td>
<td>83</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>21-82</td>
<td>76</td>
</tr>
<tr>
<td>Female Balding</td>
<td>13-51</td>
<td></td>
</tr>
<tr>
<td>Thin skin</td>
<td>84</td>
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</tbody>
</table>

Newell Price et al. 1998 Endo Rev
Endocrine Testing: CS

SCREENING

- Urine cortisol (UFC, by High Pressure Liquid Chromatography)

- Bedtime salivary cortisol (Sal F)
  Sal F, by radioimmunoassay (RIA)
  Tandem mass spectrophotometry

- 1 mg dexamethasone suppression test (DST)
Urine Free Cortisol

Yanovski, JA. JAMA 269:2232-8, 1993
Nighttime Salivary Cortisol

- healthy volunteer
- control patient
- PseudoCushing State
- Cushing’s Syndrome

Inpatients
Outpatients

Papanicolaou et al.  JCEM 87:4515-21,2002
SCS: Why is it difficult?

• The Definition
• The Confounding Comorbidities
• The Limitations of the Assays/Test
• The Clinical Relevance
• The Biases
A 59 year-old woman

- Referred for further evaluation of an adrenal mass that was discovered after she underwent abdominal CT to investigate abdominal pain

- The mass measures 1.8 x 2.5 cm and has a density of -10 Hounsfield units without contrast. The patient has a history of hypertension treated with hydrochlorothiazide. Other medications: Aspirin

- On physical examination, BMI 35. Currently normotensive

- She has prediabetes and light pink abdominal striae. Reports easy bruising.
Laboratory test results:

Glucose = 121mg/dL (7.8 mmol/L) (reference range, 70-99 mg/dL [3.9-5.5 mmol/L])

Plasma renin activity = 3.5 ng/mL per h (reference range, 0.6-4.3 ng/mL per h)

Aldosterone = 17 ng/dL (471.6 pmol/L) (reference range, 1-21 ng/dL [27.7-285.5 pmol/L])

ACTH = 12 pg/mL (2.6 pmol/L) (reference range, 10-60 pg/mL [2.2-13.2 pmol/L])

DHEA-S = 5 µg/dL (0.14 µmol/L) (reference range, 15-157 µg/dL [0.41-4.25 µmol/L])

Serum cortisol (8 AM; 1-mg overnight dexamethasone suppression test) = 5.4 µg/dL (150.0 nmol/L) (reference range, <1.8 µg/dL [<49.7 nmol/L])

Urinary cortisol = 68 µg/24 h (187.7 nmol/L) (reference range, 4-50 µg/24 h [11-138 nmol/d])

Normal Metanephrines in serum
The Definition (?)
When Do We Consider SCS?

- Evaluation of the HPA axis is abnormal
- No Clear signs of Cushing’s syndrome
- Adrenal Incidentaloma
How Frequent Is It?

- Depends on the definition
- Random cortisol
- Loss of circadian rhythm
- Blunted ACTH response to CRH
- Elevated UFC
- Abnormal Dexamethasone suppression test (varying doses)
- Altered circadian cortisol rhythm
The Confounding Comorbidities
Difficulty in Diagnosis

- Prevalence of incidentalomas increased (3-7 %) on CT scanning
- Prevalence of obesity increased
- Prevalence of Osteoporosis is high (dependent of sex, age)
- Prevalence of hypertension is close to 30 to 65 %
- Prevalence of Type II DM is 10 to 25 %
Cushing’s Syndrome and Obesity

- In the obese population the prevalence of Cushing’s syndrome is low
- Broad screening programs or having a low threshold to screen obese patients is likely not warranted
- Abnormal results should consider the possibility of a false positive test
TABLE 2. Conditions associated with hypercortisolism in the absence of Cushing’s syndrome

Some clinical features of Cushing’s syndrome may be present
- Pregnancy
- Depression and other psychiatric conditions
- Alcohol dependence
- Glucocorticoid resistance
- Morbid obesity
- Poorly controlled diabetes mellitus

Unlikely to have any clinical features of Cushing’s syndrome
- Physical stress (hospitalization, surgery, pain)
- Malnutrition, anorexia nervosa
- Intense chronic exercise
- Hypothalamic amenorrhea
- CBG excess (increased serum but not urine cortisol)

*Whereas Cushing’s syndrome is unlikely in these conditions, it may rarely be present. If there is a high clinical index of suspicion, the patient should undergo testing, particularly those within the first group.*
The Laboratory Tests
What is the Differential Diagnosis of Hypercortisolism?

What does the workup include?
Alterations in HPA axis in patient with SCS

- Debate on clinical/biochemical criteria for diagnosis

- No clinical “gold standard” parameter for diagnosis; thus expertise dependent

- Diagnosis made on at least two altered parameters; needs to be validated!!

- 1-mg overnight DST: mostly used for screening
  - NIH/AACE/AAES: 5 mcg/dL as cutoff of normal level of cortisol suppression
  - French Society of Endocrinology use lower cutoff (1.8 mcg/dL)
  - Grey area: cortisol between 1.8 and 5 mcg/dL; interpret in context of the clinical data
  - A study showed that the 8mg DST no better at diagnosing SH compared to 1mg DST.
  - 2 day low dose DST proposed to be more accurate; no definitive evidence showing its superiority.
SCS: Endocrine Testing in Suspected Cushing’s Syndrome

1-mg overnight dexamethasone suppression test (DST)

- To verify if there is loss of glucocorticoid negative feedback
- Cutoff:
  - <1.8 ug/dL (higher sensitivity/lower specificity) vs. <5 ug/dL
  - >14.3 ug/dL cortisol value → confirms CS

- False (+) 30-58% of patients with depression, schizophrenia, dementia, OCD, alcoholism in the context of old age, weight loss, sleep deprivation, medications, elevated CBG

- False (-) in nephrotic patients (lower CBG), liver/renal failure (decreased dexamethasone clearance)

Low dose 2 day DST:

- 2mg/day for 48hrs
- Better specificity but more cumbersome
- If there is 30% or more of cortisol suppression → no need to perform HDDST
Urine Cortisol

24 hr. urine cortisol (urinary free cortisol)
- High performance liquid chromatography, tandem mass spectrometry, gas chromatography coupled with mass spectrometry
- Measure 24hr urine creatinine (~20mg/kg LBW)
- Obtain a minimum of 2 samples → r/out periodic hypercortisolism
- False (+): pseudo-Cushing states, OSA, PCOS, familial glucocorticoid resistance, hyperthyroidism
- False (-): renal failure (GFR < 30 ml/min) & incomplete collection
- 1-4x ULN → r/out pseudo-Cushing
- >4x ULN → Cushing's
ACTH level \textarrow{} low (<5 pg/dL)

- Proceed with an adrenal imaging
  - CT is preferred
    - inhomogeneous mass
    - $> 10$ HU
    - bilateral vs unilateral
  - MRI help to distinguish adrenal adenoma from nonfunctioning or metastatic tumor
  - Variable, poor reproducibility (inter and intra assay)
Alterations in HPA axis in SCS

- 24hr UFC
  - By itself not adequate screening tool for SH due to its low sensitivity.
- Circadian cortisol rhythm
  - Studies reported that the MSC was not able distinguish normal from SH
- Serum ACTH:
  - not very sensitive
  - patient with ACTH independent hypercortisolism might have normal ACTH levels
- Low DHEAS

- Currently most clinicians are diagnosing on basis of: DST + UFC+ ACTH
Treatment of SCS

- Main goal → correct metabolic consequences

- No good quality prospective randomized trial available to compare surgical vs. conservative approach

  - A small prospective randomized trial → surgical treatment was better at improving HTN, DM and obesity when compared to conservative therapy

  - A retrospective trial by Chiodini et al. showed that BP and glucose levels improved s/p adrenalectomy in both patients with and without subclinical Cushings.

- Consider surgery in young patients that have vascular, metabolic and/or bone disorders that are deteriorating.

- Follow up for patient with conservative therapy:

  - No specific guidelines have been accepted
  - Expert recommendations to perform annual screening for first 5yrs with
    - UFC, 1-mg DSGT and ACTH level
    - Monitor for worsening of DM, HTN and BMD (retrospective studies)
Adrenalectomy in patients with adrenal tumors and subclinical Cushing’s syndrome

Adrenalectomy vs conservative management in patients with subclinical Cushing’s syndrome: Dichotomous outcomes.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Relative risk (95% CI)</th>
<th>Events/Group1</th>
<th>Events/Group2</th>
<th>Favors Conservative Management</th>
<th>Favors Adrenalectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenalectomy vs Conservative Management: Hypertension Improvement</strong></td>
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<tr>
<td>Chiodini</td>
<td>12.647 (0.852, 193.845)</td>
<td>8/14</td>
<td>0/10</td>
<td></td>
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<tr>
<td>Rossi</td>
<td>14.400 (0.968, 214.193)</td>
<td>4/4</td>
<td>0/7</td>
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<tr>
<td>Iacoccone</td>
<td>13.813 (0.877, 217.511)</td>
<td>8/5</td>
<td>0/12</td>
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<tr>
<td>Akaza</td>
<td>5.167 (0.654, 42.533)</td>
<td>5/5</td>
<td>0/4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guerrieri</td>
<td>27.462 (1.726, 436.947)</td>
<td>8/12</td>
<td>0/20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giordano</td>
<td>1.143 (0.026, 56.397)</td>
<td>0/6</td>
<td>0/7</td>
<td></td>
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</tr>
<tr>
<td>Tonato</td>
<td>21.053 (1.349, 331.449)</td>
<td>12/18</td>
<td>0/16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsuki</td>
<td>6.286 (0.457, 86.468)</td>
<td>5/6</td>
<td>0/3</td>
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<td></td>
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<tr>
<td>Kawate</td>
<td>9.100 (0.606, 136.688)</td>
<td>6/9</td>
<td>0/6</td>
<td></td>
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</tr>
<tr>
<td><strong>Overall (I²=0%, P=0.971)</strong></td>
<td>10.978 (4.337, 27.784)</td>
<td>56/89</td>
<td>0/84</td>
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</tr>
</tbody>
</table>

| **Adrenalectomy vs Conservative Management: Diabetes Mellitus Improvement** |
| Chiodini         | 4.375 (0.261, 68.058)   | 3/7           | 0/4           |                                |                      |
| Rossi            | 8.750 (0.615, 124.524)  | 3/3           | 0/4           |                                |                      |
| Iacoccone        | 7.000 (0.454, 101.930)  | 5/10          | 0/6           |                                |                      |
| Akaza            | 3.857 (0.269, 51.407)   | 4/6           | 0/2           |                                |                      |
| Giordano         | 1.500 (0.046, 45.070)   | 0/1           | 0/2           |                                |                      |
| Tonato           | 8.556 (0.563, 130.052)  | 5/8           | 0/6           |                                |                      |
| Tsuki            | 3.500 (0.197, 62.265)   | 2/9           | 0/6           |                                |                      |
| Kawate            | 1.647 (0.230, 12.091)   | 3/9           | 1/5           |                                |                      |
| **Overall (I²=0%, P=0.967)** | 3.915 (1.541, 9.947)   | 25/53        | 1/35          |                                |                      |

| **Adrenalectomy vs Conservative Management: Dyslipidemia Improvement** |
| Chiodini         | 1.667 (0.243, 11.448)   | 4/12          | 1/5           |                                |                      |
| Iacoccone        | 3.436 (0.201, 65.861)   | 2/10          | 0/7           |                                |                      |
| Akaza            | 4.600 (0.230, 95.117)   | 1/3           | 0/5           |                                |                      |
| Giordano         | 0.667 (0.016, 27.240)   | 0/5           | 0/3           |                                |                      |
| Tonato           | 6.222 (0.376, 102.935)  | 3/8           | 0/7           |                                |                      |
| Tsuki            | 6.500 (0.451, 93.379)   | 6/9           | 0/4           |                                |                      |
| Kawate            | 1.256 (0.092, 17.929)   | 1/8           | 1/10          |                                |                      |
| **Overall (I²=0%, P=0.917)** | 2.645 (0.969, 7.222)   | 17/55        | 2/41          |                                |                      |

| **Adrenalectomy vs Conservative Management: Obesity Improvement** |
| Chiodini         | 2.667 (0.261, 19.712)   | 4/12          | 1/8           |                                |                      |
| Iacoccone        | 10.562 (0.654, 170.561)| 6/15          | 0/12          |                                |                      |
| Akaza            | 3.333 (0.283, 36.762)   | 2/2           | 0/1           |                                |                      |
| Tonato           | 1.000 (0.023, 43.700)   | 0/6           | 0/6           |                                |                      |
| **Overall (I²=0%, P=0.778)** | 3.362 (0.945, 12.100)  | 12/35        | 1/27          |                                |                      |
Adrenalectomy vs conservative management in patients with subclinical Cushing’s syndrome: Continuous outcomes.

Cortisol as a Marker for Increased Mortality in Patients with Incidental Adrenocortical Adenomas

J Clin Endocrinol Metab. 2014 Dec; 99(12): 4462–4470.
The Biases
Spectrum Bias

- “Spectrum bias refers to the phenomenon that the performance of a diagnostic test may vary in different clinical settings because each setting has a different mix of patients”
Verification Bias

• “When the results of a diagnostic test affect whether the gold standard procedure is used to verify the test result, verification bias is introduced.”

• Also called work up bias or referral bias.

• “Verification bias is common because many gold standard procedures (i.e. adrenlectomy in SCH), such as biopsy, surgery, and angiography, are invasive, risky, and expensive.

• “Under these conditions, physicians are reluctant to refer patients for the gold standard procedure, and patients are reluctant to undergo the gold standard procedure, unless preliminary diagnostic tests have positive results”

• If the preliminary diagnostic test (i.e. 1 mg Dex) has a high false positive rate....it is a problem!
Case (Cont.)
Our Patient: Repeat Evaluation

✔ Multiple UFC:
  • 82 → 171 mcg/24hrs

✔ 1mg DST:
  • Cortisol level: 5.2 ug/dL

✔ 11pm salivary cortisol level
  • 0.09 mcg (normal is <0.09)

✔ ACTH:
  • 10 pg/mL
ASSESSMENT & PLAN:

- 1.2 cm lipid rich adrenal tumor → likely benign adrenal adenoma

- Moderate elevation of 24hrs UFC + mild elevation of midnight salivary cortisol + failed to suppress 1mg DST =
  
  **Dx: likely mild Cushing syndrome**

- Follow up with repeat 24hr UFC and ACTH in light that there are no typical cushinoid features, except mild hypertension.
Conclusions

- The diagnosis of SCS is limited by the diagnostic performance of screening test

- Symptoms and signs that may be present in SCS are common in highly prevalent disorders

- Verification and Spectrum Bias affect our ability to better understand the benefits of surgery vs. watchful waiting

- Unilateral adrenalectomy may be curative in select cases but the lack means to identify those patients who would most benefit from the procedure
Thank You