AACE MODULE

Cushing’s Syndrome

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Cushing’s Syndrome (CS): Definition

- A syndrome consisting of a large group of symptoms and signs resulting from exposure to prolonged and excessive amounts of either endogenous or exogenous glucocorticoids
Cushing’s Syndrome: History

- Cushing’s disease (CD) was first described by Harvey Cushing in 1912.
- He initially described a 23-year-old woman with obesity, hirsutism, and amenorrhea, which was later attributed to a pituitary abnormality causing adrenal hyperplasia.
Cushing’s Disease: Definition

- The term Cushing’s disease refers to pituitary dependent causes of plasma glucocorticoid excess whereas all other causes of the syndrome are described as “Cushing’s Syndrome”
Cushing’s Syndrome: Prevalence

• The most common cause of CS is exogenous use of steroids
• Endogenous Cushing’s is a rare disease
• The exact prevalence of CS is difficult to determine
• The incidence of CS in European population based studies is 2 to 3 per million

Table 1: Prevalence of Symptoms in Cushing’s Syndrome

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>91</td>
</tr>
<tr>
<td>Menstrual irregularity</td>
<td>84</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>81</td>
</tr>
<tr>
<td>Psychiatric dysfunction</td>
<td>62</td>
</tr>
<tr>
<td>Backache</td>
<td>43</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>29</td>
</tr>
<tr>
<td>Fractures</td>
<td>19</td>
</tr>
<tr>
<td>Loss of scalp hair</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs</th>
<th>Findings %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>97</td>
</tr>
<tr>
<td>Truncal</td>
<td>46</td>
</tr>
<tr>
<td>Generalized</td>
<td>55</td>
</tr>
<tr>
<td>Plethora</td>
<td>94</td>
</tr>
<tr>
<td>Moon facies</td>
<td>88</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74</td>
</tr>
<tr>
<td>Bruising</td>
<td>62</td>
</tr>
<tr>
<td>Red-purple striae</td>
<td>56</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>56</td>
</tr>
<tr>
<td>Ankle edema</td>
<td>50</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3: Prevalence of Signs in Cushing’s Syndrome

<table>
<thead>
<tr>
<th>Other Findings</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>74</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50</td>
</tr>
<tr>
<td>Overt</td>
<td>13</td>
</tr>
<tr>
<td>Impaired glucose tolerance test</td>
<td>37</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>50</td>
</tr>
<tr>
<td>Renal calculi</td>
<td>15</td>
</tr>
</tbody>
</table>

Cushing’s Syndrome: Discriminating Features

• Although the features listed in Tables 1 thru 3 are suggestive of CS, the presence of proximal muscle weakness, easy bruisability, plethora, purple striae and hypertension in a patient are particularly helpful in increasing the suspicion for CS.
Cushing’s Syndrome – Causes

- ACTH dependent:
  - Cushing’s disease (pituitary dependent)
  - Ectopic ACTH syndrome
  - Ectopic CRH syndrome
  - Macronodular adrenal hyperplasia
  - Iatrogenic (Treatment with ACTH)
Cushing’s syndrome – Causes

• ACTH Independent:
  iatrogenic- use of exogenous steroids (most common)
  Adrenal adenoma or carcinoma
  Primary pigmented nodular adrenal hyperplasia and Carney’s syndrome
  McCune Albright syndrome
Cushing’s Syndrome: Diagnosis

• The diagnosis of CS is made in two steps:

1. Establish the presence of CS (hypercortisolism)

2. Determine the source of excessive cortisol secretion
Cushing’s Syndrome: Diagnosis (Step 1)

Who should be tested for hypercortisolism?

- Patients with clinical features suggestive of CS (see tables 1-3)
- Patients with unusual features for age (osteoporosis, hypertension)
- Children with growth retardation and increased weight
- Patients with incidentally discovered adrenal tumors (incidentalomas)
- Patients with metabolic syndrome
- Patients with hypogonadotrphic hypogonadism.
- Polycystic ovarian syndrome

Nieman LK; et. al. The diagnosis of Cushing’s Syndrome: An Endocrine Society Clinical Practice Guideline. JCEM 2008;93(5):1526-1540
Findling JW; et. al. Screening and Diagnosis of Cushing’s Syndrome. Endocrinol Metab Clin N Am 34 (2005): 385-402
Cushing’s Syndrome: Screening Tests

• One of the following tests should be performed as an initial test to establish the diagnosis of Cushing’s:
  1. One mg overnight dexamethasone suppression test (DST)
  2. 24-hour urinary free cortisol (UFC)
  3. Midnight salivary cortisol
  4. Two mg DST over 24 hours for 2 days
Cushing’s Syndrome: One mg Dexamethasone Suppression Test

- Administer 1 mg of dexamethasone (Dex) at 2300 and measure plasma cortisol at 0800 the following morning.
- Normal response: Plasma cortisol should be less than 1.8 mcg/dL (sensitivity > 95%, specificity = 80%)
- The old cut off value of 5 mcg/dL following 1 mg Dex is not currently used.
- Drugs including estrogens may affect results.

JCEM 2008;93:1526-1540
Wood PJ et al Ann Clin Biochem 1997;34 (pt 3) 222-229
Cushing’s Syndrome: 24-hour Urinary Free Cortisol

- 24-hour urine is collected for estimation of free cortisol.

- Urinary creatinine should always be obtained to confirm adequate collection.

- Normal cut off value depends on the methods used to estimate free cortisol. A value higher than 4 times normal is diagnostic of CS.

- Test is unaffected by drugs which increase cortisol binding globulins (CBG) but may be affected by other drugs.

- Due to variability of hypercortisolism in Cushing’s at least two measurements of 24-hour UFC should be performed.
Cushing’s Syndrome: Midnight Salivary Cortisol

- Saliva is collected between 2300-2400 hours by passive drooling or by placing a cotton pledget in the mouth and chewing for 1-2 minutes.
- The sample is stable at room temperature or refrigerator for several weeks.
- Using an ELISA or LC-MS/MS assay the normal cut off values are less than 145 ng/dl.
- Sensitivity of 92-100%, and specificity of 93-100% have been described.
- Due to variability of hypercortisolism in Cushing’s at least two measurements of salivary cortisol should be performed.

LC-MS/MS = Tandem mass spectrometry. The diagnosis of Cushing’s syndrome. JCEM 2008;93:1526-1540
Cushing’s Syndrome: 2 mg Dexamethasone Test

- Dex is given as 0.5 mg every 6 hours, beginning at 0900, i.e. 0900, 1500, 2100 and 0300 hours for 2 days

- Plasma cortisol is then measured at 0900, 6 hours after the last dose of Dex

- A cut off value of 1.8 mcg/dl has a sensitivity of greater than 98% and specificity of 97 to 100%* has been reported

- Due to the inconvenience of Dex administration for two days, some endocrinologists consider this as a second line test**

** Pivonello et al. Endocrinol Metabolic Clinic N Am 2008;37;135-149
Cushing’s Syndrome: Drug Interference

• Several drugs may interfere with the testing for Cushing’s

• Drugs that increase Cortisol binding globulin (CBG) and may falsely elevate cortisol results:
  Estrogens
  Mitotane

JCEM 2008;93:1526-1540
Cushing’s Syndrome: Drug Interference

• Drugs that accelerate dexamethasone metabolism by induction of CYP3A4:
  
  Phenobarbital  Ethusuximide
  Phenytoin      Pioglitazone
  Rifampin      Rifapentine
  Carbamazepine Primidone

• These drugs may result in false positive results when using dexamethasone

• It is therefore suggested by some that levels of dexamethasone should be measured to confirm adequate plasma concentration of dexamethasone (0.22 mcg/dl) but this is not widely practiced.

JCEM 2008;93:1526-1540
Cushing’s Syndrome: Drug Interference

- Drugs that impair dexamethasone metabolism by inhibition of CYP3A4:
  - Aprepitant / Fosaprepitant
  - Itraconazole
  - Ritonavir
  - Fluoxetine
  - Diltiazem
  - Cimetidine

- These drugs may cause a false negative result in tests using dexamethasone
Cushing’s Syndrome: Drug Interference

- **Drugs that increase urinary free cortisol results:**
  Carbamazepine
  Fenofibrate (if measured by HPLC)
  Some synthetic glucocorticoids (if measured by RIA)

- **Drugs that inhibit 11 beta-hydroxysteroid dehydrogenase:**
  Licorice
  Carbenoxolone
Cushing’s Syndrome: Localization of Hypercortisolism (Step 2)

- When the presence of CS is confirmed, obtain ACTH levels

- If ACTH level is suppressed (<5 pg/ml) - adrenal dependent Cushing’s

- If ACTH level is not suppressed (>15 pg/ml) - investigate ACTH dependent causes

- If ACTH level is between 5 and 15 pg/ml - doubtful further testing is needed (see algorithm)
Cushing's Syndrome: Algorithm for Localization

- **ACTH Level**
  - > 15 pg/ml (ACTH-dependent)
  - 5-15 pg/ml
  - < 5 pg/ml (ACTH-independent)

**High Dose Dexamethasone Suppression Test**
- (8 mg po overnight test or 2mg q6hours for 48 hours)
  - > 50% serum cortisol suppression
- **OR**
- **CRH Stimulation Test**
  - > 20% increase above basal serum cortisol post CRH
  - > 35% increase above basal serum ACTH post CRH

- **Yes**
  - Cushing’s Disease
  - MRI Scan Pituitary
  - **Surgery for Operable Tumor**

- **No**
  - BIPSS with CRH
    - (Bilateral inferior petrosal sinus sampling)
    - **Gradient**
      - (BIPSS to peripheral ACTH ratio > 2 in the basal state &/or > 3 after CRH suggest CD)
    - **No Gradient**
      - **CT/MRI**
        - (Neck/Chest/Abdomen/Pelvis) or Octreotide Scan
        - **EAS Localized**
          - Surgery for Operable Tumor
        - **EAS Not Localized**
          - Follow-up & Reimage

*If there is a high suspicion for EAS skip BIPSS and continue EAS algorithm*
Cushing’s Syndrome: Determining the source

- High dose dexamethasone suppression test
  - Give Dex 2 mg orally every 6 hours for 8 doses
  - Draw a cortisol level at 2 or 6 hours after the last Dex dose
  - A plasma cortisol suppression above 50% suggests CD

- CRH stimulation test
  - Obtain baseline cortisol and ACTH* level
  - Administration of 1 µg/kg or 100 µg of CRH
  - Draw a cortisol at 30 and 45 minutes
  - A mean increase of cortisol > 20%
    (and a mean increase of ACTH* > 50%) above baseline suggests CD

- Bilateral inferior petrosal sinus sampling (IPSS)
  - Experienced radiologist catheterizes both IPSS
  - ACTH samples at 3, 5, and 10 minutes after CRH simultaneously from both IPS and a peripheral vein
  - An IPSS to peripheral ACTH ratio > 2.0 in the basal state and/or > 3.0 after CRH suggests CD

* Obtaining ACTH level is optional and provides additional confirmation
Pseudo-Cushing’s Syndromes

- Refers to conditions associated with some or all of the clinical features of CS with some evidence of hypercortisolism
- Resolution of the underlying causes results in disappearance of Cushingnoid state
- A 2mg Dex/CRH test is useful in differentiating Pseudo-Cushing’s from CS
Pseudo-Cushing’s Syndrome

Causes

- Pregnancy
- Depression
- Alcohol dependence
- Glucorticoid resistance
- Morbid Obesity
- Poorly controlled diabetes mellitus
- Physical stress (Hospitalization, surgery, Pain)
- Malnutrition, anorexia nervosa
- Intense chronic exercise
- Hypothalamic amenorrhea
- CBG excess (Increased serum cortisol but not UFC)

Adapted from JCEM 2008;93:1526-1540
Cushing’s Syndrome: 2 mg Dex /CRH Test

- Administer 2 mg of Dex for two days followed by CRH (1 mcg/kg IV) 2 hours after the last dose of dex
- Cortisol is measured every 15 minutes later for one hour
- A normal response <1.4 µg/dl excludes Pseudo cushing’s
- Sensitivity = 98%
- Specificity = 70%

Nieman, L. Editorial JCEM 2007;92:2876-2878
Subclinical Cushing’s Syndrome

- Occurs in patients with clinically not apparent adrenal adenomas that become minimally autonomous for cortisol secretion, only partially restrained by pituitary feedback.
- Clinical stigmata of Cushing’s are absent but high prevalence of Obesity, hypertension and type 2 diabetes.
- Diagnosis: Low ACTH level; Loss of diurnal variation; Inadequate cortisol suppression with overnight 1 mg DST or 2 mg DST.

Cyclical Cushing’s Syndrome

• Cyclic CS is a phenomenon of intermittent hypercortisolism in a cyclic pattern with peaks occurring at intervals of several days to years.
• Cortisol stimulation and suppression tests may give spurious results.
• Frequent measurement of 24-hour UFC or salivary cortisol may be the best mode for diagnosis.
Cushing’s Syndrome: Treatment

- Surgical treatment is recommended for all patients with endogenous CS

- Transphenoidal pituitary resection for pituitary dependent causes. Unilateral adrenalectomy for adrenal adenoma
  Bilateral adrenalectomy for failed pituitary surgery
  Resection of tumors for EAS or bilateral adrenalectomy for palliation

- Persistent and recurrent hypercorticolism have the following options:
  Repeat Surgery
  Radiation Therapy
  Medical Therapy
  Bilateral adrenalectomy- Risk of development of Nelson’s syndrome (concomitant pituitary macroadenoma, high plasma ACTH levels with resultant skin pigmentation.)
Cushing’s Syndrome: Medical Treatment

• Adrenal blocking agents
  A. Inhibitors of Adrenal Steroidogenesis:
     Metyrapone
     Ketoconazole
     Aminoglutethemide
  B. Adrenolytic:
     Mitotane

• Neuromodulatory Drugs (dopamine agonist):
  Bromocriptine
  Cabergoline
Cushing’s Syndrome: Follow-up

- Monitor for hypopituitarism after surgery for CD.
- Most patients receive perioperative glucocorticoids, withdraw steroids when stable in about 3-6 months after surgery and assess for cortisol deficiency.
- Monitor for relapse with 24-hour UFC or 2 mg DST.
- Monitor for Nelson’s syndrome after bilateral adrenalectomy (if present pituitary radiotherapy is indicated).