Challenges in Diagnosing and Localizing Cushing’s Syndrome

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NJ AACE
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Memorial Sloan Kettering Multidisciplinary Pituitary & Skull Base Tumor Center

Multidisciplinary program that provides comprehensive and integrated delivery of care for patients with pituitary tumors and pituitary disorders.

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Objectives of presentation

• When should we suspect Cushing’s and how do we differentiate true Cushing’s from pseudo-Cushing’s?

• How do we confirm the diagnosis?

• How do we localizing the source?
THE
PITUITARY BODY
AND ITS
DISORDERS

CLINICAL STATES
PRODUCED BY DISORDERS OF THE
HYPOPHYSIS CEREBRI

BY
HARVEY CUSHING, M.D.

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PROFESSOR OF SURGERY (LECT) HARVARD UNIVERSITY

AN AMPLIFICATION OF THE HARVEY LECTURE
FOR DECEMBER, 1910

229 ILLUSTRATIONS

PHILADELPHIA & LONDON
J. B. LIPPINCOTT COMPANY
Case: O.K.

- 38 year-old woman presented with weight gain, trouble sleeping, irregular periods, and hirsutism. She had been noting symptoms for a number of years.

- Recent medical history significant for rising BP and elevated fasting glucose

- PE: BMI 40; BP 140/90, overall obesity, round face, mild ‘buffalo hump,’ but no supraclavicular fullness, striae, or obvious muscle weakness
Case: O.K. continued

- Urine free cortisol 65 μg/24 hr (<50μg/24 hr)

- Midnight salivary free cortisol 0.12 and 0.08 (mcg/dl) (<0.09)

- 1 mg dexamethasone suppressed serum cortisol 3.3 μg/dl (<1.8 μg/dl)

- Plasma ACTH 46 pg/ml (<52 pg/mL)

- Fasting glucose 110
Identifying Cushing’s in the era of obesity: cortisol’s anabolic & catabolic effects

- **Anabolic**: Obesity, insulin resistance

- **Catabolic**: Osteoporosis, muscle atrophy (proximal muscle weakness), thin skin, easy bruisability

“With the rapid increase in the rate of obesity in the general population, Cushing’s syndrome can no longer be reliably separated from the metabolic syndrome of simple obesity on the basis of anabolic signs alone.”

Lynn Loriaux *NEJM* 2017; 376:1451-9
Figure 1. Measurement of Skinfold Thickness.
Skinsfold thickness is measured with a caliper and a micrometer or millimeter ruler (Panel A). A skinfold is created (Panel B) and measured with the caliper (Panel C). The thickness of the skinfold is read on the ruler; the thickness is 3 mm in this case (Panel D).
Thin skin = thickness of < 2 mm; if found the positive likelihood ratio of CS is 116.
Signs & Symptoms Specific for Cushing’s

- Easy bruising (3+ non-traumatic ecchymoses larger than 1 cm)
- Proximal muscle weakness
- Wide (>1cm) pigmented striae
- Osteoporosis, hypokalemia (if no other cause)

- If thin skin, osteopenia, ecchymoses are present, probability of Cushing’s is 95% (per Loriaux)

- Can also be present but not as predictive: Obesity, HTN, Oligo-amenorrhea, hirsutism, acne, insulin resistance, kidney stones, neurocognitive manifestations, insomnia
First rule out exogenous exposure

- Oral
- Injected – back, joints, muscle – can stick around
- Topical (fluocinolone)
- Inhaled (beclomethasone)
- Medroxyprogesterone acetate (Depo-Provera)

- Some patients do not realize the treatment (injection, cream etc.) contains glucocorticoids; or don’t mention unless asked

- Testing will show low ACTH, serum and urine cortisol; erratic values
Consider Pseudo-Cushing’s
physiologic causes of hypercortisolism

• Depression & other psychiatric conditions
• Severe obesity
• Alcoholism
• Poorly controlled diabetes mellitus
• Pregnancy
• Glucocorticoid resistance
• Physical stress (hospitalization, etc.)
• Hypothalamic amenorrhea/anorexia/intense exercise
• CBG excess

Will not have clinical features of Cushing’s

- High cortisol levels, but not as high as true CS, UFC ≤ 4x normal
- Usually no cutaneous or muscle signs
- Resolves when treat underlying condition
Diagnosis needs to be established before localization

1. Does the patient have Cushing’s?

2. Is it ACTH-dependent or ACTH-independent?

3. What is the source of the Cushing’s?
Does the patient have Cushing’s?
clinical findings + 2 abnormal diagnostic tests

• Document cortisol hypersecretion:
  • 24 hr. urinary free cortisol (UFC)

• Loss of normal diurnal rhythm:
  • Late night salivary free cortisol

• Cortisol autonomy/abnormal negative feedback:
  • Lack of suppression after low dose dexamethasone

Does the patient have Cushing’s?
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Does the patient have Cushing’s: 24 hr. UFC

- Direct reflection of free bioactive serum cortisol
- Not affected by CBG level
- Normal range 10-55 µg/day with HPLC/MS
- If 3-4x ULN = Cushing’s; otherwise repeat x 2-3
- Mild/intermittent CS can have 1+ normal UFC
  - Results are variable and depend on assay used
  - Single test low sensitivity (normal with disease)
- Pseudo-CS can have mildly increased UFC

Kidambi S Eur J Endocrinol 2007; Elias PC JCEM 2014; Raff JCEM 2015; Elamin JCEM 2008; ; Petersenn S Clin Endocrinol 2014
Caveats to the 24 hr. UFC

• Falsely high with large urine volume (> 5L/day)
• Falsely low with GFR <30 ml/min
• Confirm adequacy of collection with creatinine levels
  • >1.5 g per day for man, 1 g for woman
• Affected by some drugs & steroids
  • RIA affected by cortisol metabolites and synthetic GCs
  • Carbamazepine & fenofibrate interfere with HPLC; licorice & carbenoxolone inhibit 11B-HSD2 -> cause falsely high values
• Cumbersome for patients; needs to be refrigerated

Mericq MV J Clin Endocrinol Metab 1998;
Chan KC Clin Chem 2004
Does the patient have Cushing’s?

- Document cortisol hypersecretion
- **Loss of normal diurnal rhythm**
- Lack of suppression with low dose dexamethasone
Loss of diurnal rhythm: LN salivary cortisol

- Very easy to do; repeat 2-3 times
  - Before brushing teeth
  - Chew on cotton, put in tube; stable at room temperature
- High sensitivity & specificity (93-100%)
- Normal levels exclude diagnosis in most cases
- Helpful with early or cyclic disease
  - Usually abnormal when UFC is normal or mildly abnormal in proven CS
- Cut-off depends on assay

Meikle Clin Endocrinol 1982; Putignano P JCEM 2003; Kyriazopouloub JCEM 1992
Late night salivary cortisol caveats

• Age, hypertension, diabetes may increase salivary cortisol

• Circadian rhythm altered with shift work, new time zone
  – Avoid time travel & stress immediately before collection

• Licorice and tobacco inhibit 11B-HSD2 in salivary glands and can increase salivary cortisol

• Immunoassays may increase false positive rate
  – Possibly due to cross-reactivity with cortisone

Liu H *Clin Endocrinol* 2005; Baid *JCEM* 2007
Does the patient have Cushing’s?

- Document cortisol hypersecretion
- Loss of normal diurnal rhythm
- Lack of suppression with low dose dexamethasone
Dexamethasone suppression test: GC negative feedback

• **1 mg overnight DST**
  • 1 mg dex at 11pm; check 8 am ACTH, cortisol, dex level
  • Cortisol >1.8 µg/dl abnormal -> need further testing (higher cut-off: > 5 µg/dl less sensitive/more FN )
  • High false positive rate (30%)

• **classic 2 day low dose DST (↑specificity)**
  • 0.5 mg q 6 hours x 48 hours (8 doses)
  • Start at noon
  • Check cortisol at 8am on last day (2 hours after last dose)
  • Check baseline 24hour UFC and second 24hrUFC on second day of test (normal <10)
  • Cortisol < 1.8 µg/dl excludes CS in 90% of cases; <5 most cases
Comments on low dose dex

• Diagnostic test for adrenal Cushing’s
• May be better than UFC for pseudo-CS:
  • HPA activation not autonomous
• Stop ocps or HRT 6 weeks before (increased CBG)
  • Not a good test during pregnancy
• Medications affecting CYP3A4 can increase or decrease dex metabolism, causing FP or FN results:
  • Phenytoin, rifampin, carbamazepine, phenobarbital, ETOH -> check dex level!
• Renal & hepatic failure decrease dex clearance
• 3-8% CD suppress on low dose: FN’s

What if the patient has minimum clinical features and/or discordant or mildly abnormal test results?

• Repeat tests

• Serial testing and clinical assessments over time: true Cushing’s progresses

• Conduct additional neuroendocrine testing

Case: O.K. continued

- 1 mildly elevated 24 hr. UFC
- 1 of 2 high LNSC
- Normal/slightly high post-dex serum cortisol (depending on cut-off used)
- Next step: repeat tests
  - Repeat urine free cortisol 124 μg/24 hr (<50μg/24 hr)
  - Midnight salivary free cortisol 0.20 and 0.14 (mcg/dl) (< 0.09)
  - Second plasma ACTH 65 pg/ml (<52 pg/mL)
- Diagnosis confirmed: ACTH-dependent Cushing’s
Pseudo vs. true Cushing’s: Dex-CRH test

- LDDST (0.5mg p.o. q6h), start at noon
- Then give CRH (100 µg IV) at 8am (2h after last dose of dex); check cortisol 15 min later
- Adenomas will respond to CRH while suppressed by dex (more resistant to suppression)
- Serum cortisol > 1.4 µg/dl (38 nmol/L) = true CS

Yanovski JA...Nieman LK et al. *JAMA* 1993; 269:2232
Localization

• 1. Does the patient have Cushing’s?
  – Document cortisol hypersecretion
  – Loss of diurnal rhythm
  – Lack of suppression on low dose dex
  – Dex-CRH

• 2. Is it ACTH-dependent or independent?

• 3. What is the source of the Cushing’s?
Causes of Cushing’s Syndrome

Cushing’s Syndrome (endogenous)

ACTH-dependent: 80-85%
- Pituitary (CD) 80% (70% of total) F:M 6:1
- Ectopic ACTH 20% (10% of total) More males
- Adrenal adenoma 60% (10% of total)
- Adrenal carcinoma 40% (5% of total)

ACTH-independent: 15-20%
- Small-cell lung Carcinoma (20-50%)
- Bronchial Carcinoid (2-40%)
- Rare:
  - Macronodular hyperplasia
  - PPNAD
  - MAS
ACTH-dependent or -independent?

- Check ACTH & cortisol at least twice on separate days
- Late afternoon; best time 11p-12a; draw on ice
- **ACTH < 5 pg/ml** (with cortisol >15) = ACTH-independent (adrenal)
- **ACTH >15 pg/ml** = ACTH-dependent (pituitary, ectopic)
- Between 5-15 pg/ml not definitive but *usually* ACTH-dependent
  - ACTH can be normal with ACTH dependent disease
- Adrenals often nodular/asymmetric with ACTH-dependent disease
Localizing ACTH-dependent disease

• If ACTH-dependent
  – Women: 90% are pituitary (pre-test likelihood)
  – Men: 60% are pituitary

• 1. **HIGH** dose dexamethasone suppression

• 2. CRH test

• 3. Image Pituitary

• 4. IPSS (if needed)
Localizing ACTH-dependent disease:
High dose dex suppression

- In theory: Cushing’s disease will suppress, ectopics will not

- Overnight 8 mg test: give 8mg dex at 11p-12a, am cortisol <5 µg/dl c/w CD

- 2-day test: collect baseline 24hr UFC, then 2 mg dex q6 x 8 hours; continue 24 hr UFC
  - CD: UFC <5 (<90% of baseline), cortisol & ACTH undetectable
HDDST caveats

• 80% of CD: cortisol suppress <50% baseline -> less than pre-test likelihood (for woman)

• ACTH-secreting bronchial carcinoids (1/2 of all cases of ectopic ACTH secretion) can present like pituitary CD (less severe presentation than other ectopic tumors)
  – May suppress with high dose dex
  – Small (1cm) & slow growing; insidious onset

• Some cases of pituitary Cushing’s do NOT suppress with high dose dex
  – Most cases that do NOT suppress turn out to have pituitary Cushing’s (60-70%)
  – Macroadenomas may need higher doses to suppress
Localizing ACTH-dependent disease: CRH test

- CRH causes exaggerated response in pituitary vs. ectopic tumors
- Pt fasts for 4 hours. ACTH drawn at -5, 0, 15, & 30 min; cortisol drawn at -15, 0, 45, & 60 min after CRH (100 µg)
- 35% increase in ACTH or 20% increase in cortisol -> almost 100% specificity (some ectopic tumors respond)
- Expensive & complicated
- SE: mild brief facial flushing
Localizing ACTH-dependent disease: pituitary MRI

- Pituitary MRI (with gadolinium) after prior tests

- 10-25% of population has an incidental pituitary adenoma so MRI does not help in diagnosis of CS, just localization

- 85-95% ACTH tumors are microadenomas

- 40% of pituitary CD will have a normal MRI

- If pituitary MRI normal/microadenoma -> Inferior petrosal sinus sampling (IPSS) to localize
Localizing ACTH-dependent disease: IPSS

- When should IPSS be done?
  - ACTH-dependent disease, but nothing seen on MRI, or only a small adenomas seen
    - Pituitary adenoma > 6mm-10mm seen -> don’t need IPSS (plus other tests supporting CD)

- Best test to distinguish CD from ectopic

- Not good for lateralization (60-70% accurate)
Localizing ACTH-dependent disease: IPSS procedure

- Identifies pituitary as source in a patient who has already been diagnosed with Cushing’s
  - Does NOT differentiate CD from normal or pseudo-CS

- Collect 24 hr UFC (or salivary cortisol) day before to confirm hypersecretion at time of test

- 4 sets of 3 simultaneous samples drawn from inferior petrosal sinuses & peripheral vein: 2 sets immediately before and 3, 5, 10, 15 min after injecting 100 µg CRH

- CD (& normal): ACTH central: peripheral basal ratio >2:1, stimulated ratio >3:1
Back to the case: IPSS
Figure 4. Maximal Ratio of Corticotropin in Inferior Petrosal Sinus Plasma to Corticotropin in Peripheral Plasma in Patients with Cushing’s Syndrome, Ectopic Corticotropin Secretion, or Adrenal Disease.

Panel A shows the results of corticotropin measurement in basal samples, and Panel B shows the results in samples obtained after the administration of corticotropin-releasing hormone (CRH). Corticotropin measurement after CRH administration is superior to basal measurement for differentiating Cushing’s syndrome from ectopic corticotropin secretion and primary adrenal disease. Five patients with primary adrenal disease had undetectable corticotropin in peripheral plasma before and after CRH administration (asterisks in Panels A and B). The positive predictive value of this test is 1. Data are from Oldfield et al.25
Localizing ACTH-dependent disease: IPSS complications

- 0.2% incidence CVA
- Rare:
  - transient cranial nerve palsy
  - DVT/PE
- 20% incidence:
  - Inguinal hematoma
  - Transient cardiac arrhythmia
  - Perforation of right atrial wall
- Needs to be done at an experienced center
ACTH-dependent disease: Ectopic Cushing’s

- If IPSS does not show a central-peripheral ACTH gradient
  - CT chest -> abdomen -> pelvis -> neck
  - Octreotide scanning
  - Gallium 68 (DOTATATE)

- Tumor types:
  - Small cell lung carcinoma
  - Neuroendocrine tumors (bronchial carcinoids, thymic carcinoids, pancreatic NETs, medullary thyroid carcinomas, pheochromocytomas)

- 9-27% NETs remain occult (tumor cannot be localized)

Sequential detection & confirmation for localizing Ectopic Cushing’s

Clinical Suspicion of Ectopic Cushing’s Syndrome

- Positive exam
- Negative exam

Octreoscan
- Positive in 66% of cases with negative CT or MRI; lowest FPs

Total body CT scan
- Helpful in 35% of cases with negative CT

FDG-PET
- Gallium-PET unavailable consider Octreoscan

Gallium-PET

Start Treatment

Consider Treatment

Re-evaluation New PET-CT scan during follow-up

Isidori et al JCEM 100: 3231-3244, 2015
ACTH-independent disease

• Thin-section CT (or MRI) of adrenals
  – BL hyperplasia seen with ACTH-dependent disease (esp ectopic) and ACTH-independent BL macronodular hyperplasia

• Adrenal adenomas usually smaller than carcinomas & have lower un-enhanced CT attenuation value (HU) and rapid contrast washout (>60% at 15 minutes)

• Necrosis, hemorrhage, calcification c/w carcinoma

• Adrenal imaging NOT useful with ACTH-dependent disease
  – 70% have enlarged adrenals
    • 20% of these have nodules > 1 cm
Summary of Diagnostic tests: (does not involve imaging)

• 2 best initial tests for ACTH-dependent disease:
  – 24-hour urine free cortisol
    • 3-4x ULN = Cushing’s, otherwise repeat x3 (misses early/cyclic CS)
  – 11pm-12am salivary cortisols: repeat 2-3 x

• If mildly abnormal/normal, & strong clinical suspicion: Repeat tests!

• Low dose dexamethasone suppression test
  – 1 mg overnight - high FP’s, good for adrenal incidentalomas, D/C ocps
  – 0.5 mg q 6 hours x 8 doses - high FN’s
  – Morning cortisol > 1.8 µg/dl is abnormal

• Dex-CRH: pseudo vs. true CS
Summary of algorithm for localization

Confirmed Cushing’s syndrome
ACTH (two measurements)

<10 pg/mL (<2.2 pmol/L)
ACTH independent
CT or MRI of adrenals

Primary adrenal disorders:
unilateral mass-adrenal adenoma or carcinoma;
Bilateral abnormalities-macronodular
or micronodular hyperplasia

Women: 90% are pituitary
Men: 60% are pituitary

40% of pituitary CD have
normal MRI

10-20 pg/mL (2.2-4.4 pmol/L)
CRH test to differentiate the
two forms

>20 pg/mL (>4.4 pmol/L)
ACTH dependent

MRI pituitary
HDDSST ↔ CRH test
(desmopressin test)

Adenoma
<6 mm
Discordant tests

Adenoma >6 mm
and concordant
tests

BIPSS

CT or MRI
(neck, chest, abdomen and pelvis)

Complementary imaging
octreo scan, PET or PET-CT

Ectopic ACTH
tumour

Positive
Negative
Follow-up re-imaging

Positive
Surgery

Negative

Cushing’s disease
confirmed

Lacroix, Feelders, Stratakis, Nieman *Lancet* 2015; 386:913-27
Treatment algorithm for CD

- Cushing's disease established
  - TSS by expert neurosurgeon
    - Persist or recurrent CD?
      - (+) Consider repeat TSS
      - (-) Monitor for recurrence

- Consider interim medical therapy in severely ill patients or when delays until surgery are anticipated

- Persistent or recurrent CD, not surgical candidate
  - Treat acute/life threatening complications
  - Pre-surgery
  - Awaiting the effects of radiotherapy
  - Adenoma in an unfavorable location
  - Consider bilateral adrenalectomy
  - Consider radiation therapy with interim medical therapy
  - Consider medical therapy*
There is a need for medical therapy

- Remission rates after transsphenoidal surgery:
  - Microadenoma: 65 - 90%; macroadenoma: < 65%

- Recurrence up to 25-40% after 5 years

- Success rates after second TSS 20-60%

- Fractionated external beam radiotherapy achieves control of hypercortisolemia in 50-60% within 3-5 years

- Bilateral adrenalectomy associated with 8-38% risk of Nelson’s syndrome
Drug targets for Cushing’s disease

- Somatostatin analogs
- Dopamine agonists (Retinoic acid)
- Ketoconazole
- Etomidate
- Metyrapone
- Mitotane (LCI699)
- Glucocorticoid receptor antagonists
- Mifepristone
Sloan Kettering Pituitary Center resources

- **Weekly multi-disciplinary pituitary & skull base clinic**
- **Bi-weekly Pituitary Tumor Board**
  - Pituitary/skull base cases discussed with neuroendocrine, neurosurgery, neuroradiology, neuro-oncology, interventional radiology, and radiation oncology colleagues
- **Pituitary rotation for endocrine fellows**
- **Clinical trials for new medical therapies for Cushing’s and acromegaly**
  - Levoketoconazole for Cushing’s
  - LCI699 for Cushing’s
  - Oral and SC somatostatin for acromegaly
- **Ongoing pituitary studies**
  - Longitudinal cohort study of patients with Cushing’s assessing the role of excess cortisol in the regulation of adipose tissue, metabolic profile, and long term risk
  - Study investigating mechanisms of ACTH tumor development
Thank you

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