Cushing’s Syndrome: Diagnostic and Treatment Dilemmas

Kristen Riley, MD and Brooks Vaughan, MD
UAB Neurosurgical Pituitary Disorders Clinic
Objectives

- Review the most recent information regarding the diagnosis and source localization of Cushing’s syndrome and disease
  - Causes, including genetics
  - Suspicion/Screening
  - PseudoCushing’s
  - ACTH dependence
  - Adrenal Cushing’s
  - IPSS/ectopic disease
  - Medical therapies
  - Adrenalectomy
  - Assessment/Monitoring for Cure
Causes of Cushing’s Syndrome/Disease

- Pituitary-Dependent Cushing’s Syndrome
  - 60-80% of cases (lower in children)
  - Approximately 1 per million per year
  - More common in women than men
  - Corticotroph adenoma (hyperplasia debated)
  - Most microadenomas (10% macros)
  - Carcinomas described
<table>
<thead>
<tr>
<th>Genetic Syndromes: CD</th>
<th>Gene</th>
<th>Function</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carney complex (typically ACTH-Indep.)</td>
<td>PRKAR1A</td>
<td>TSG</td>
<td>Myxomas, endo tumors, skin</td>
</tr>
<tr>
<td>DICER1</td>
<td>DICER 1</td>
<td>TSG</td>
<td>Pituitary blastoma</td>
</tr>
<tr>
<td>FIPA</td>
<td>AIP</td>
<td>TSG</td>
<td>Isolated pit. Adenoma</td>
</tr>
<tr>
<td>McCune-Albright (typically ACTH-Indep.)</td>
<td>GNAS (mosaic mutation)</td>
<td>Oncogene</td>
<td>PFD, café-au-lait, hyperfunction</td>
</tr>
<tr>
<td>MEN1</td>
<td>MEN 1 (AD)</td>
<td>TSG</td>
<td>Parathyroid, GINET</td>
</tr>
<tr>
<td>MEN2A</td>
<td>RET (AD)</td>
<td>Oncogene</td>
<td>MTC, pheo</td>
</tr>
<tr>
<td>MEN2B</td>
<td>RET (AD)</td>
<td>Oncogene</td>
<td>MTC, pheo, neuroma</td>
</tr>
<tr>
<td>MEN4</td>
<td>CDKN1B (AD)</td>
<td>TSG</td>
<td>MEN1-like</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1/C2 (AD)</td>
<td>TSG</td>
<td>Hamartomas</td>
</tr>
<tr>
<td>USP8</td>
<td>Somatic</td>
<td>Deubiquitinase</td>
<td>CD</td>
</tr>
</tbody>
</table>

Approximately 1/3 of cases may be due to activation of USP8

- Deubiquitinase which leads to increase of the EGF receptor on corticotrophs
- May represent a therapeutic target (inhibition of USP8 or EGFR)
- Mutation leads to enhanced proteolytic cleavage and catalytic activity of USP8
- Enhanced promoter activity of the gene encoding proopiomelanocortin

Ectopic ACTH/ Ectopic CRH

- Diverse tumor types
  - Small-cell lung cancer
  - Bronchial Carcinoid
- CRH producing tumors
  - 20 in literature, many also make ACTH
ACTH Independent

• Varied group
  • Adrenal adenoma
  • Adrenal carcinoma
  • Bilateral Macronodular Adrenal Hyperplasia (rare and genetics now well defined)
  • McCune-Albright
  • Primary pigmented nodular adrenal disease (PPNAD)
    • Often in context of Carney Complex (PRKAR1A mutation)
Screening

Challenge is two-fold:
- We don’t want to miss cases (population-based screening is likely not worthwhile, even in DM2 and obesity due to prevalence)
- We don’t want to over-diagnose
- No testing is perfect
- Historical attempts to devise an “index” have failed (poor predictive values)
- Are there other/novel ways to strengthen diagnostic accuracy?
Whom to suspect?

• AACE study on claims
  • 2015 Study of co-morbid conditions associated with Cushing’s syndrome and Relative Risk
  • Matched Case-Control study of a commercial insurance claims database
  • Conditions and dyad combinations among patients with CD and non-CD controls

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized adiposity</td>
<td>∞</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>61</td>
</tr>
<tr>
<td>Facial plethora</td>
<td>21</td>
</tr>
<tr>
<td>PCOS</td>
<td>14.8</td>
</tr>
<tr>
<td>Abnormal weight gain</td>
<td>11.2</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9.3</td>
</tr>
<tr>
<td>DVT</td>
<td>7.5</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>7.3</td>
</tr>
<tr>
<td>Female balding</td>
<td>7</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>5.3</td>
</tr>
<tr>
<td>Condition 1</td>
<td>Condition 2</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>Serious infection</td>
<td>Adrenal mass</td>
</tr>
<tr>
<td>DM2</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>DM2</td>
<td>Early menopause</td>
</tr>
<tr>
<td>Weakness/fatigue</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Adrenal Mass</td>
</tr>
<tr>
<td>DM2</td>
<td>Adrenal Mass</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>Serious infection</td>
<td>Hirsutism</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>Adrenal mass</td>
</tr>
</tbody>
</table>
Screening for Cushing’s Disease

- Once you have clinical suspicion: three primary modalities
  - Late night salivary cortisol
  - Dexamethasone suppression test (1 mg)
  - 24 hour urine free cortisol and creatinine
- At least two of three positive
- When screening, sensitivity favored over specificity

Endocrine Society Guidelines: The Diagnosis of Cushing’s Syndrome, 2008
Nuances of Each Screening Test

- **Salivary Cortisol**
  - Normal ranges vary by lab
  - Abstain from smoking for 24 hours (?) although convincing proof of this need is lacking
  - Blood (?)
  - Tobacco/licorice (false elevation?)
  - Hand contamination (Dog’s ear cream)

Endocrine Society Guidelines: The Diagnosis of Cushing’s Syndrome, 2008
Nuances of Each Screening Test

• 1 mg DST
  • Cannot be done if on exogenous estrogen due to CBG effects (50% false positive)
  • Current cutoff 1.8 µg/dl (95% sensitivity, 80% specificity)
  • At 5 µg, 95% specificity
  • Sensitivity/specificity sliding scale
  • Meds can alter metabolism of dexamethasone (phenytoin, carbamazepine, rifampicin)
  • Draw dexamethasone level to ensure adequate concentration (normal vary)

Endocrine Society Guidelines: The Diagnosis of Cushing’s Syndrome, 2008
24 hour urine free cortisol

- Free level, not affected by CBG
- May be normal in mild disease
- High if urine volume is high
- Low if creatinine clearance is low (less than 60 ml/min)
- Correct technique is key
- Normal value does not rule out Cushing’s
- AUC, may be the last to become abnormal
Diagnosis

- Two clearly abnormal tests are sufficient for diagnosis, move to supplementary or localizing tests
- PseudoCushing’s is an exception
- In typical patients:
  - Two negative tests and low suspicion, discontinue evaluation
  - Two negative tests and high suspicion, follow and repeat

Endocrine Society Guidelines: The Diagnosis of Cushing’s Syndrome, 2008
Other Screening Tests

- Liddle’s 48h, 2 mg DST
  - No improvement in sensitivity or specificity over other tests
- Dexamethasone CRH test
  - Similar sensitivities and specificities to available tests for screening
- Midnight Serum Cortisol
  - 48 hour admission to avoid false positive, may not be possible, very good sensitivity and specificity
- Desmopressin stimulation test
  - No improvement in sensitivity or specificity

Endocrine Society Guidelines: The Diagnosis of Cushing’s Syndrome, 2008
PseudoCushing’s

- Uniquely challenging
- “Clinicians who have never missed the diagnosis of Cushing’s syndrome or have never been humbled by attempting to establish its cause should refer their patients to someone who has”

PseudoCushing’s

- This term may not be used precisely.
- Can describe those with Cushingoid features with no evidence of Cushing’s.
- More precisely use to describe those with hypercortisolism that is non-neoplastic (may be physiologic).
- These patients may or may not have phenotypic features of Cushing’s syndrome.
## PseudoCushing’s

### Potential Causes of Non-Neoplastic Cushing’s Syndrome

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism and withdrawal</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>Depression and neuropsychiatric disease</td>
</tr>
<tr>
<td>Glucocorticoid resistance</td>
</tr>
<tr>
<td>DM2, uncontrolled</td>
</tr>
<tr>
<td>Starvation- different phenotype</td>
</tr>
<tr>
<td>Pregnancy- different phenotype</td>
</tr>
<tr>
<td>Chronic intense exercise- different phenotype</td>
</tr>
</tbody>
</table>

PseudoCushing’s

• We now have a variety of sensitive screening tests, ruling Cushing’s out has become more straightforward

• Specificity is the struggle

• Concern for cyclic disease: repeat the testing until reassured

• Imaging has no role in the differentiation of Cushing’s and PseudoCushing’s

• Remind yourself where you are in the process (screening vs localizing)
### Screening Tests and Alternate Tests

<table>
<thead>
<tr>
<th>Test for Cushing’s</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivary cortisol</td>
<td>92-100%</td>
<td>93-100%</td>
</tr>
<tr>
<td>1 mg DST</td>
<td>95%</td>
<td>80 (1.8 µg/dl)-95 (5µg/dl)%</td>
</tr>
<tr>
<td>24 hr UFC</td>
<td>89% ULN</td>
<td>95-100% (higher as it rises)</td>
</tr>
<tr>
<td>48 h, 2mg DST</td>
<td>95%</td>
<td>70-96%</td>
</tr>
<tr>
<td>Dex-CRH</td>
<td>86%</td>
<td>70-100%</td>
</tr>
<tr>
<td>Midnight serum cortisol: sleeping</td>
<td>100%</td>
<td>87%</td>
</tr>
<tr>
<td>Midnight serum cortisol: awake</td>
<td>96%</td>
<td>83-96%</td>
</tr>
<tr>
<td>Desmopressin stimulation</td>
<td>82-87%</td>
<td>85-91%</td>
</tr>
</tbody>
</table>

Endocrine Society Guidelines: The Diagnosis of Cushing’s Syndrome, 2008
PseudoCushing’s

• No test is perfect
• Sometimes more testing is “kicking the can down the road”
• Not helpful to do more tests that don’t improve specificity
• No real issues with sensitivity with current testing
• Human factor is unavoidable
Screening Complete and Positive: Determine Cause

• ACTH dependent vs Independent
  • ACTH can be checked anytime despite the fact that we have normal diurnal pattern, but if low repeat in AM
  • Less than 5 pg/ml is adrenal, over 20 pg/ml is ACTH dependent
  • 5-15 pg/ml equivocal (most will be ACTH dependent)

Endocrine Society Guidelines: The Diagnosis of Cushing’s Syndrome, 2008
Determine Cause

• CRH stimulation can be useful if ACTH is equivocal (5-15 pg/mL)
• Adrenal and ectopic ACTH secreting tumors should suppress gland, no CRH response
• Cutoffs vary (35 % ACTH rise, 20 % cortisol an example)
• Positive response is very specific for pituitary Cushing’s but some pituitary tumors don’t respond.
• In some series, 0 ectopic ACTH-secreting tumors responded (very good specificity for pituitary Cushing’s)
Determine Cause

- DHEA-S can be helpful
- Suppressed in adrenal Cushing’s (ACTH is relatively suppressed)
- Normal/high in pituitary and ectopic ACTH secretion

Endocrine Society Guidelines: The Diagnosis of Cushing’s Syndrome, 2008
Adrenal (ACTH Independent) Cushing’s

• Imaging is next step, CT if not contraindicated
• If unilateral nodules, address surgically (a bit different from hyperaldosteronism- AVS in Cushing’s is not well validated)
• Can consider unilateral vs bilateral adrenalectomy in bilateral disease
  • PPNAD
  • BMAH

ACTH Dependent Cushing’s

• Further Localization: Determine Pituitary vs. Ectopic Disease
• Controversy:
  • Use of supplementary tests vs use of IPSS
  • Need for further testing with visible adenoma
• IPSS is the gold standard but not widely available
• Lab testing is not as accurate as we’d like
• MRI may be as specific as labs under certain circumstances
• Clinical characteristics of the individual patient’s disease can help
<table>
<thead>
<tr>
<th>CD</th>
<th>Ectopic ACTH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Gradual</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Female &gt; male</td>
</tr>
<tr>
<td><strong>Hypokalemia</strong></td>
<td>Uncommon (&lt;10%)</td>
</tr>
<tr>
<td><strong>Random Cortisol</strong></td>
<td>Under 50 mcg/dL</td>
</tr>
<tr>
<td><strong>UFC</strong></td>
<td>Less than 10x</td>
</tr>
<tr>
<td><strong>ACTH</strong></td>
<td>Usually &lt; 200 pg/mL</td>
</tr>
<tr>
<td><strong>POMC / other ACTH pre...</strong></td>
<td>Usually not elevated</td>
</tr>
<tr>
<td><strong>MRI Pituitary</strong></td>
<td>≥6mm tumor helpful</td>
</tr>
<tr>
<td><strong>8 mg DST</strong></td>
<td>≥69% suppression</td>
</tr>
<tr>
<td><strong>CRH stim</strong></td>
<td>≥35% increase ACTH,</td>
</tr>
<tr>
<td></td>
<td>≥25% increase in cortisol</td>
</tr>
<tr>
<td><strong>IPSS</strong></td>
<td>Pre CRH ACTH IPS:P ratio ≥2</td>
</tr>
<tr>
<td></td>
<td>Post CRH ratio ≥3</td>
</tr>
</tbody>
</table>

Testing to establish the cause of Cushing's syndrome*

ACTH: corticotropin; CRH: corticotropin-releasing hormone; CT: computed tomography; MR: magnetic resonance; MRI: magnetic resonance imaging; dexamethasone; IPSS: inferior petrosal sinus sampling.

*Testing can only be interpreted in the context of sustained hypercortisolism and may be inaccurate with cyclic hypercortisolism.
MRI Specificity

- Tumor 6mm or greater may provide 96% Specificity for ACTH secreting pituitary adenoma (some unpublished data may contradict)
- This may be higher than the specificity of the HDDST (80% accuracy in some series)
- May be higher than the specificity of the DEX-CRH test (7-14% of CD do not respond, 10% of bronchial carcinoids may)

Pituitary MRI Findings in Patients with Pituitary and Ectopic ACTH Syndrome: Does a 6 mm Tumor.. Endocrine Practice. October 2015, 21 (10) 1098-1103.
Argument Against HDDST

Fig. 1 Percentage of baseline of serum cortisol levels 48 h after 2 mg/d dexamethasone (LDDST 48 h) or 8 mg/d dexamethasone (HDDST 48 h) according to the etiology of CS. (Reproduced with permission from Isidori AM et al. (2003) J Clin Endocrinol Metab 88:5299–5306)
ACTH-Dependent Cushing’s Disease

• Diagnosis made
• Next step, if pituitary would be transsphenoidal surgery
• Would recommend high volume surgeon
• Dr. Riley to discuss
• Will move to post-operative evaluation
Predictors of Remission and Recurrence

- 8113 treatment naïve patients:
  - Remission rate after TSS 71% for adults
  - 21% failure of surgery
  - Recurrence after successful TSS 13%
  - Size of tumor was the only statistically significant predictor of remission

How to Define Remission and Recurrence

- Exact timing of post-operative assessment is not universally agreed upon.
- Some dogma that if POD #1 is elevated, go immediately back to OR.
- Would make that decision in context.
- We have seen POD #1 numbers that were suggestive of persistent disease fall.
- POD 2-3 may have value.
- Adrenal autonomy is possible.

Immediate Post-Op Decisions

- Post-op plans: we tend to decide in the context of the patient
- Tumor size
- What was seen in the OR?
- Comorbidities
- Patient preference
- Severity of disease
Delayed Remission?

- Seen in 5.6% of 620 patients in one series

Examples of individual time courses of UFC after TSS

Pt ID #18

Pt ID #22

Pt ID #15

UFC Z-score vs. Follow Up Day

## Medical Therapies: Adrenolytic Agents

<table>
<thead>
<tr>
<th>Medical therapy</th>
<th>Pros</th>
<th>Cons</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Quick onset, relatively inexpensive, oral</td>
<td>Harder to get, black box warning re: hepatic failure/death</td>
<td>400-1600 mg q 6-8 h</td>
</tr>
<tr>
<td>Metyrapone</td>
<td>Quick onset, oral</td>
<td>Hard to get, hypokalemia, liver toxicity</td>
<td>500 mg-6g/day Q 6-8 hours</td>
</tr>
<tr>
<td>Mitotane</td>
<td>FDA approved liver cancer, adrenolytic</td>
<td>Slow to work, severe GI side effects</td>
<td>250 mg to start, 500-8 mg per day</td>
</tr>
<tr>
<td>Etomidate</td>
<td>IV, quick onset</td>
<td>ICU monitoring</td>
<td>Bolus, titrate</td>
</tr>
</tbody>
</table>
# Medical Therapies: Other

<table>
<thead>
<tr>
<th>Medical therapy</th>
<th>Pros</th>
<th>Cons</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone (Korlym)</td>
<td>Oral, effective</td>
<td>Hard to titrate, hypokalemia, no biomarker, endometrial thickening</td>
<td>600-900 mg BID</td>
</tr>
<tr>
<td>Pasireotide (Signifor)</td>
<td>Hyperglycemia, good biomarker</td>
<td>Best for mild disease, pituitary only, twice daily (may change). LAR approved in acromegaly</td>
<td>600-900 µg BID</td>
</tr>
</tbody>
</table>

Denis Ciato, Aizhar G. Mumbach, Marcelo Paez-Pereda & Günter K. Stalla (2017) Currently used and investigational drugs for Cushing’s disease, Expert Opinion on Investigational Drugs, 26:1, 75-84
Adrenalectomy for Cushing’s Disease

• Reminder that cure rates for microadenomas are 80-90% and less than 60% for macroadenomas even for experienced surgeons
• Combined cure rates around 79%
• We discuss transsphenoidal surgery as part of a spectrum of options initially, including medical therapy and adrenalectomy

Kelly DF. Transphenoidal Surgery for Cushings: Review of Success rates. Neurosurgery Focus. 2007; 23 (3)
Understandable historical reluctance:

- Surgical Morbidity/Mortality
  - Has improved
- Nelson’s syndrome
  - Can be managed
- Quality of life
  - Similar to successful transsphenoidal surgery
Adrenalectomy

- Laparoscopic is as effective with shorter hospital stays
- Retroperitoneal approach avoids repositioning
- Must remove gland en bloc - if capsule is broken, can spill cells that can become recurrent disease
- Ectopic tissue can cause disease

Nelson’s syndrome

• Defined as pituitary adenoma enlargement after adrenalectomy
• Can occur in 8-25% (one study 50%) of patients with adrenalectomy and no radiation
• Radiation clearly lowers this risk (numbers vary dramatically from 50-100% reduction)

Nelson’s Syndrome

- Typically characterized by very high (800-25000 pg/mL) ACTH levels
- Difficult to cure if it expands sella, becomes locally invasive
- Concern about transformation into carcinoma
- Surgery recommended before it becomes a macroadenoma
- Serial MRI can prevent this occurrence
- Can occur in 8-25% (one study 50%) of patients with adrenalectomy and no radiation
- Radiation clearly lowers this risk (numbers vary dramatically from 50-100% reduction)

Quality of Life Post-Adrenalectomy

• One retrospective review of 40 patients 3m-10y post adrenalectomy:
  • Zero operative mortalities
  • 8% Nelson’s treatment
  • 91% would do the adrenalectomy again
  • 81% fell into upper 2/3 of national average for mental and physical composite scores
  • No deaths from adrenal insufficiency

On To Dr Riley

• Should be time for discussion during cases
Imaging

- MRI with contrast with focused views of sella
- 1.5T most common
- 3T may be useful if 1.5T negative
- Dynamic sequences useful
- Volumetric 3D- GRE shows hypointensity of adenoma due to delayed contrast wash in
- With increased strength imaging may increase rate of false positive scans
Obvious versus subtle findings
Imaging references

Inferior Petrosal Sinus Sampling

Credit for slides to Dr. John Deveikis, UAB
Indications for IPSS

- ACTH dependent Cushing’s syndrome.
- MRI negative or equivocal.
- Post-op persistence of Cushing’s.
Venous drainage of pituitary
Inferior petrosal sinus sampling

- Right and left femoral venous sheaths.
- Catheters advanced through venous system, up the jugular veins and into each inferior petrosal sinus.
- Contrast injections confirm proper catheter placement and also exclude confounding venous anomalies.
- Simultaneous blood samples are obtained from the right and left IPS and also a peripheral sample from the femoral sheath.
Inferior petrosal sinus sampling

- Sets of venous samples for ACTH are obtained for baseline, then at selected intervals after pituitary stimulation, usually ovine CRH (1 μg/kg up to 100).
- Samples are carefully labeled, put on ice, and rushed to the lab.
- Procedure takes 1-2 hours and patient is observed for 3 hours, then discharged.
IPSS evaluation

• Compare IPS to peripheral ACTH (IPS:P).
• Ratio 2:1 IPS:P before CRH: 95% sensitive, 100% specific for Cushing’s disease\(^1\)
• 3:1 IPS:P post-CRH: 100% sensitive, 100% specific for Cushing’s\(^1\)
• 1.4:1 side to side threshold gives lateralization 68% pre and 71% post-stimulation\(^1\)

In this day of medication shortages:

• DDAVP (10 μg IV) can be used instead of CRH: 92.1% sensitive and 100% specific, and lateralization confirmed in 97.8%¹

• Not ready for prime-time: DDAVP can be prothrombotic.²

Illustrative Case

- 44 year old man with fatigue, weight gain
- Lab tests show elevated cortisol and elevated ACTH
- Cushing’s disease suspected
- MRI showed no apparent pituitary tumor
- Venous sampling was requested
Case: IPSS
### Case Results: ACTH pre-and post- DDAVP stimulation

<table>
<thead>
<tr>
<th>Time</th>
<th>-15 min</th>
<th>-10 min</th>
<th>-5 min</th>
<th>+1 min</th>
<th>+3 min</th>
<th>+5 min</th>
<th>+10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIPS</td>
<td>505</td>
<td>378</td>
<td>606</td>
<td>6658</td>
<td>15300</td>
<td>18250</td>
<td>18000</td>
</tr>
<tr>
<td>LIPS</td>
<td>42</td>
<td>51</td>
<td>38</td>
<td>288</td>
<td>923</td>
<td>1153</td>
<td>1075</td>
</tr>
<tr>
<td>Peripheral</td>
<td>19</td>
<td>24</td>
<td>19</td>
<td>21</td>
<td>36</td>
<td>93</td>
<td>235</td>
</tr>
</tbody>
</table>

Deveikis IPSS 11-9-2015
Case results

- RIPS & LIPS greater than 2X peripheral pre stimulation (40 or 500 vs. 19).
- RIPS and LIPS greater than 3X peripheral post stimulation (1100 or 18,000 vs. 90).
- This gives nearly 100% certainty source is pituitary.
- RIPS greater than 1.4X LIPS (18,000 vs. 1100).
- This gives at least 71% certainty lesion is on the right.
- Confirmed at surgery

Deveikis IPSS 11-9-2015
IPSS: fewer false negatives than pituitary MRI, but not perfect

### TABLE 3: Diagnostic Performance Figures of BIPSS in Previous Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample Size/Successful Catheterization</th>
<th>CRH or CRH Plus Desmopressin</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>False-Negatives</th>
<th>False-Positives</th>
<th>No Final Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oldfield et al. [12]</td>
<td>281/278</td>
<td>262</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Lopez et al. [19]</td>
<td>32/30</td>
<td>24</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopman et al. [20]</td>
<td>501</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaltsas et al. [5]</td>
<td>128/86</td>
<td>118/6a</td>
<td>97</td>
<td>100</td>
<td>2</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Wiggam et al. [21]</td>
<td>53/38</td>
<td>2</td>
<td>82</td>
<td></td>
<td>3</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Bonelli et al. [1]</td>
<td>92/82</td>
<td>92</td>
<td></td>
<td>90</td>
<td>6</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Lefournier et al. [18]</td>
<td>86/82</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Sweeringen et al. [22]</td>
<td>179/143</td>
<td>120</td>
<td>90</td>
<td>67</td>
<td>8</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Our study</td>
<td>78/66</td>
<td>25/53b</td>
<td>94.4</td>
<td>62.5</td>
<td>2</td>
<td></td>
<td>3b</td>
</tr>
</tbody>
</table>

Note—BIPSS = bilateral inferior petrosal sinuses sampling; CRH = corticotropin-releasing hormone.

a In this study, 118 patients received stimulation with CRH, six patients with CRH plus desmopressin, and four patients with desmopressin alone.

b Twenty-five patients underwent stimulation with CRH alone and 53 with CRH plus desmopressin.

c False-positives and specificity were calculated including three patients with adrenocorticotropic hormone–independent Cushing’s syndrome.


Deveikis IPSS 11-9-2015
False negatives with IPSS

- Occurs in 1-10% of cases presumably from imperfect sampling technique or venous anomalies.\(^1\text{-}^4\)

- Can use prolactin (PRL) as a marker that pituitary venous drainage is adequately sampled. Basal IPS:P (PRL) >1.8 indicates good sampling of pituitary blood. \(^5\)

- Ratio of peak IPS:P (ACTH) to basal IPS:P(PRL)> 0.8 in proven Cushing’s vs <0.6 in ectopic ACTH. \(^5\)

IPS entry variants


Deveikis IPSS 11-9-2015
Anatomic variant: IPOV

- Inferior petro-occipital vein.
- Channel parallel to IPS under the skull-base.
- Commonly present, but only 10% communicate with cavernous sinus.\(^1\)
- May provide an additional option to access cavernous sinusous blood.\(^2\)


Deveikis IPSS 11-9-2015
IPS and IPOV

Deveikis IPSS 11-9-2015
Complications of IPSS

- In experienced hands, neurological complications in 0.083%\(^1\)
- Less experienced, smaller series have higher neurological complications.
- A small series of 34 had two (5.9%) DVT and one death.\(^2\)

Brainstem ischemia after IPSS: 1 of 44 cases (2.3%)

Avoiding complications of IPSS

- Systemic heparinization.
- Gentle manipulation of catheters and gentle contrast injections.
- Keep an eye on the patient.
- Permanent deficits can be avoided if the catheter is quickly withdrawn if patient develops severe pain, dizziness, nausea, numbness, diplopia, or hypertension.¹

Conclusions: IPSS

- In *carefully selected patients*, IPS sampling can be a helpful diagnostic tool with high degree of accuracy and safety in experienced hands.
- Otherwise, try jugular venous sampling.
Surgery

- Transnasal, transsphenoidal
- Endoscope versus microscope
- Sphenoid anatomy variations
- Perioperative concerns in the Cushing’s patient
  - HTN, obstructive airway, cardiopulmonary issues, cerebrovascular disease
Endoscopic Transssphenoidal approach
Sphenoid Pneumatization

- Presellar and sellar: 80%
- Postsellar: 17%
- Conchal: 3%
  -- Completely nonpneumatized

Figures from Endoscopic Pituitary Surgery, Cappabianca and de Divitiis
23 yo F presented w/anxiety, difficulty concentrating

ACTH secreting macroadenoma

Pre and Post-op
Resection of small macroadenoma - ACTH secreting
Surgery: cure rates

- Postop remission reported 60-90%
- Late recurrence reported 10-65%
- Examples of variation in reporting:
  - Cleveland Clinic: micro: 89%, macro 63%
  - Multicenter Retrospective review 8 centers: 41%
  - Postoperative cortisol levels < 2-5, variable decrease over first 72 hrs

WHO classification of tumors of the pituitary gland

- 2004
  - Adenoma (typical)
  - Atypical Adenoma
  - Carcinoma

- Atypical: definition was vague ("atypical morphological features suggestive of aggressive behavior such as invasive growth")
  - "other features including elevated mitotic index and a Ki-67 labeling index greater than 3% as well as extensive nuclear staining for p53 reactivity"
  - Variable incidence due to use of different criteria depending on center
  - Have seen that not all atypical tumors are clinically aggressive
– Somatotroph adenoma
– Lactotroph adenoma
– Thyrotroph adenoma
– **Corticotroph adenoma**
– Gonadotroph adenoma
– Null-cell adenoma
– Plurihormonal and double adenoma

– Pituitary carcinoma +CSF and/or systemic metastasis

– Pituitary blastoma- rare, primitive, malignant; typically infants under 2yo, present with signs/symptoms of Cushing’s disease

Important changes

• Principle guiding classification: the pituitary adenohypophyseal cell lineage
• Use immunohistochemistry with immunostains
• Transcription factors when needed (PIT-1, SF-1, T-PIT)
  • T-PIT antibodies not currently reliable/available
• Description of histopathology, mitotic index, Ki-67 labeling index and invasiveness should be considered for prediction of clinical aggressive behavior

Transcription factors

- PIT-1: somatotrophs, lactotrophs, thyrotrophs, plurihormal
- SF-1: gonadotrophs
- T-PIT: corticotrophs

Increased probability for recurrence

- Elevated proliferative activity
- Variants:
  - Sparsely granulated somatotroph adenoma
  - Lactotroph adenoma in men
  - Silent corticotroph adenoma
  - Crooke cell adenoma
  - Plurihormal PIT-1 positive adenoma

Radiosurgery

• Goal: **precise** and **efficient** delivery of radiation to a specific target

• Types:
  • Gamma Knife- radioactive cobalt-60 source. Frame based treatment, utilizing helmet with 192 collimators
  • LINAC- delivery of high energy radiation by a linear accelerator, in combination with stereotactic localization, called radiosurgery, typically frameless
    • Cyberknife, Trubeam, Edge
UAB Gamma Knife Procedures

- 1995-2013
- 205 pituitary tumors treated with radiosurgery
  - 92 macroadenomas
  - 113 functional
Optic Nerve Proximity
Outcomes

(No evidence of superiority of different types of radiosurgery)

- Multicenter analysis of 278 pt with CD, GK only
  - Initial control of hypercortisolemia 80% at 10 yrs
  - 18% recurrence
  - Overall, 64% control at 10 years
  - Mean time to normalization 14.5 months
  - New endocrinopathy 25% (systemic assessment after RS not done at all centers)
  - New cranial neuropathy 3%
  - Tumor control rate 95%

- Review of 21 studies, 706 pt with CD, all modalities of RS
  - Remission reported from 25-80% with follow up 2-17 years
  - Median time to normalization 12-25 months
  - New endocrinopathy 0-66%
  - Tumor control rate 82-100%


Break prior to case discussions
Case 1
Presented 2006, 34yo WF

- 34yr h/o hirsutism, acne, 100lb wt gain
- Amenorrhea x 16 months
- 6yo child, 3 early miscarriages
- 24hr UFC 217 µg (nl <45 µg)
- Abnormal dex suppression test
- MRI normal
- IPSS positive, lateralized to Right
- Repeat MR, possible adenoma on Right
- OR Jan 2006: no obvious tumor, did hypophysectomy
- Path: ACTH+microadenoma
Follow up

• 2007, 2009
• Appears biochemically cured, weight down, on hydrocortisone, levothyroxine and desmopressin
• MRI stable, no tumor

• 2012: Feb recurrent clinical symptoms, weaned and stopped hydrocortisone MRI normal
• March: 24 hr UFC and salivary cortisol WNL
• June: elevated 24hr UFC and abnormal dex suppression test
• MRI normal
What Would You Do Now?

- Factors
  - Female?
  - Age (now 40)
  - Patient preference
Case 1

- July 2012: repeat pituitary surgery, no tumor found in sella
- Continues to be hypercortisolemic
- What would you do?
Case 1

- July 2013: bilateral adrenalectomies
- Improved until August 2015
- Symptoms began to return (?)
- Feb 2016: documented elevated cortisol, ACTH levels over 200 pg/mL
- Note, also has ITP
- What would you do?
Case 1 Continued

- CT abdomen reveals a “pea sized” mass in area of L adrenal, likely ectopic adrenal tissue
- Surgeon not comfortable with resection
Case 1 Continued

- May 2016: MRI with right cavernous sinus tumor
- May 2016: pituitary surgery, ACTH + adenoma
Tumor in sella and right cavernous sinus 2016 preop

Postop 2016
Case 1 Continued

- Ideas?
Radiosurgery

- No additional surgical options for pituitary tumor in cavernous sinus
- Planned Radiosurgery

- Pituitary 20 Gy, single fraction
  - September 2016
- Adrenal tissue, 13 Gy x 3 fractions, total 39 Gy
  - November 2016
- Prior to December 2016: fatigue, nausea, decreased cortisol levels, improved on hydrocortisone
  - Cortisol from 107→ 1.6 mcg/dL
Radiosurgery plan:
20 Gy prescription dose
Optics receive less than 8-10 Gy
13Gy x 3 fx, cumulative 39Gy to adrenal beds
2017

• Became very Cushingoid on excessive hydrocortisone, up to 100mg/day - not physician prescribed dosing
• Started somatotropin for pan-hypopituitarism (along with LT4, estrogen, cortisol) Oct 2017
• Nov 2017: subjectively improved, losing weight, on hydrocortisone 10/5/5
• MRI: decreased tumor size in right cavernous sinus
Case 2
33yo WF

- Presente with acute, severe HA, N/V. HA lasted 1 wk. Seen by PCP who noted asymmetric pupils and ordered MRI. Referred to Pituitary clinic
- Initial history: HTN dx 3 years prior, regular menstrual cycle, no weight gain, + hirsutism, not Cushingoid
- Passed cortisol stimulation testing, due to hirsutism, planned dexamethasone suppression testing
- ACTH 183 pg/mL
- 24hr UFC 2 x upper limit of normal, cortisol 14 mcg/dL after 1mg dex suppression
• Other clinical findings:
  – Hyperpigmentation
  – Glucose intolerance
  – No weight gain due to obsessive exercise
MRI
Case 2

- Endocrinologist recommended transsphenoidal surgery
- Did not do supplemental biochemical testing
Treatment

- Surgery for tumor resection with nasoseptal flap for skull base repair
Postoperatively

- POD 1 ACTH: 83 pg/mL; cortisol: 27 mcg/dL
- Pathology: ACTH + pituitary adenoma
- Placed on hydrocortisone postoperatively (due to large tumor needing NSF received stress dose in OR)
Case 2

• Based on POD #1 Labs, what are your thoughts?
Case 2

- Weaned and failed cortisol stimulation test 2 months postoperatively, failed 3x more in 2 years (repeated due to concern of likely recurrence based on POD#1 labs)
- Clinically: decreased Cushingoid appearance, 15lb weight loss without exercise, decreased hyperpigmentation
- Elected to treat with adjuvant radiation due to residual tumor in left cavernous sinus
Follow up

- Received 50.4 Gy in 28 fractions
- 1 yr post XRT - started on levothyroxine
- Stable years 2-4 post XRT
- Year 5 post decreased IGF1, irregular menstrual cycles (now 39)
- Started on somatotropin; estrogen/progesterone for decreased ovarian reserve
- Salivary cortisol normal in Jan 2018
Case 3
77 yo F presented w/weight gain
Diagnosed with Cushing’s disease (outside endo)
Clinically improved, labs show no evidence of Cushing’s

1st surgery attempt cancelled due to very labile HTN, returned 3 wks later, underwent surgery Path: ACTH+ pituitary adenoma
3 months post op

No laboratory evidence of recurrent Cushing’s

9 months post op
11 months postop

GK considerations:
Proximity to optic pathways: nerves and chiasm

Dose considerations: treat as functional or nonfunctional?
Treatment

20 Gy to 50% isodose line
98% of tumor rec’d 12 Gy
94% tumor rec’d 20 Gy
Max dose on left optic nerve 9 Gy
Max dose to chiasm 4 Gy
Long term follow up

- 3 yrs after radiosurgery recurrent Cushing’s
- Now 81 yo
Case 3

- What would you do?
- Ongoing Cushing’s s/p surgery and GK
- 81 years old?
Case 3

- Started on ketoconazole
- 5 months later, clinically declining and shortly after passed away
Case 4
60 yo WF

- Hospitalized at OSH with CHF, HTN, labs and physical exam c/w Cushing’s syndrome
- Pituitary clinic workup c/w ACTH dependent Cushing’s disease
- Dex suppression 11 mcg/dL with positive dex level
- Salivary cortisol 0.19 mcg/dL (normal less than 0.09 mcg/dL)
- ACTH 28-42 pg/mL
- 24 urine cortisol reported as high, never obtained, Dr. Vaughan did not feel it would change management
MRI - Normal, No Visible Adenoma
Case 4

• How do you feel about decision to omit the 24 hour urine cortisol?
• 3 Tesla MRI?
• What would you do next?
Cortisol 20.7 mcg/dL at +10 min

ACTH levels (pg/mL)
(*100 mcg CRH given*)

<table>
<thead>
<tr>
<th>TIME</th>
<th>-15</th>
<th>-10</th>
<th>-5</th>
<th>+1</th>
<th>+3</th>
<th>+5</th>
<th>+10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right IPS</td>
<td>41</td>
<td>46</td>
<td>40</td>
<td>117</td>
<td>378</td>
<td>212</td>
<td>190</td>
</tr>
<tr>
<td>Left IPS</td>
<td>28</td>
<td>29</td>
<td>24</td>
<td>25</td>
<td>35</td>
<td>38</td>
<td>49</td>
</tr>
<tr>
<td>Peripheral</td>
<td>27</td>
<td>26</td>
<td>22</td>
<td>24</td>
<td>37</td>
<td>27</td>
<td>33</td>
</tr>
</tbody>
</table>

Findings: Results approach threshold of 2:1 central:peripheral ratio before CRH and exceed 3:1 ratio after CRH. This indicates a pituitary source of ACTH with high confidence. Right side was consistently higher, indicating a right sided source with at least 70% confidence. Summary: IPSS results compatible with pituitary source of ACTH, likely on the right
Treatment

• Surgery: explored gland, found suspicious area at right side of gland. Pathology did not demonstrate tumor

• Postop Day 1 0800
  • Cortisol- 7.5 (preop at 12:30 53.9)
  • ACTH- 11

2 years out, off cortef, no evidence of recurrence
15yo WM

• HTN x 2 yrs
• Weight gain
• DM type II
• Evaluation c/w Cushing’s disease
• MRI normal
### IPSS results

**ACTH levels (pg/mL)**

(98 mcg CRH given *)

<table>
<thead>
<tr>
<th>TIME</th>
<th>-10</th>
<th>-5</th>
<th>0</th>
<th>+1</th>
<th>+3</th>
<th>+5</th>
<th>+10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right IPS</td>
<td>189</td>
<td>677</td>
<td>586</td>
<td>52</td>
<td>1063</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>Left IPS</td>
<td>44</td>
<td>60</td>
<td>68</td>
<td>3556</td>
<td>1636</td>
<td>1237</td>
<td>1101</td>
</tr>
<tr>
<td>Sheath</td>
<td>57</td>
<td>62</td>
<td>57</td>
<td>59</td>
<td>69</td>
<td>65</td>
<td>74</td>
</tr>
</tbody>
</table>

The side to side measurements are inconsistent between pre-and post-CRH, but since a follow-up venogram on the right indicated that the catheter was out of position for at least some of the pre-CRH samples it would be reasonable to disregard the pre-CRH lateralization. Left side was consistently higher after CRH indicating a left sided source with approaching 70% confidence.
Identified tumor in OR, path ACTH + pituitary adenoma

Postop Day 1 0800
- ACTH 42 pg/mL
- Cortisol 5.3 mcg/dL

3 months postop, tapered off hydrocortisone, failed cort stim, 6 months postop passed cort stim
Case 5

• Is he at risk for recurrence?
67yo WF with eye pressure, Dizzy x 2 yrs

- Saw ENT, imaging demonstrated pituitary lesion (2013)
- Outside endocrinologist- “all pituitary labs normal except ACTH 107”, included UFC
- 24 hour urine cortisol repeatedly normal (18-28 mcg/24 hours, normal <45). Had a salivary cortisol 2 years ago, not repeated
- Outside surgeon rec’d observation, came to UAB for second opinion
- Note some tumor growth since 2013, no visual changes referable to tumor (some glaucoma changes)
- Offered surgery due to growth, pt declined
- 2016-17 MRI stable
Late 2017 - 8 months since prior visit

- Pt seen by UAB Spine Neurosurgery for evaluation of neck pain
- Noted “progression of alopecia, striae and buffalo hump concerning for Cushing’s”
- Seen by Dr Vaughan, updated labs: Cortisol 9.7 mcg with dex level of 250 ng/dL
- Salivary cortisol high x 2 (0.11 and 0.14 mcg/dL (normal less than 0.09 mcg/dL)
- Have recommended surgery (visual change plus convincing adenoma)
Case 6

- When monitoring for recurrence, progression, or in setting of high suspicion, favor sensitivity over specificity