Cushing’s Disease: Diagnostic and Management Dilemmas

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Disclosures

• Corcept
  – Speaker’s Bureau and Consultant

• Pfizer
  – Speaker’s Bureau
Cushing’s Disease

pituitary over-production of ACTH

excess cortisol
Cushing’s Disease: Clinical Features

- Incidence: 0.7 to 2.4 new cases per million/yr
- Female preponderance: 68-87%
- Mean age 35 – 40 years
- Four-fold increase in mortality, related to cardiovascular complications and abnormal glucose metabolism
The major challenges with Cushing’s Disease:

- Does the patient have Cushing’s disease?
- Where is the tumor?
- Assessing for remission and monitoring for recurrence
- Management of recurrent disease
Does the patient have Cushing’s disease?
“It’s 2 for Cushing’s and 2 against! We need another opinion.”
Spectrum of Clinical Presentation is Broad

Sub-clinical cushing’s

Diagnosis should be made clinically and biochemically, not radiographically

No screening test is perfect

Sometimes the patient knows best…
Case 1: S.M.

**History:** 37 year old woman with 85 lb weight gain over 7 years, despite rigorous diet/exercise. Recent onset of Hypertension

**Exam:** Central Obesity, Mild Dorso-cervical and supraclavicular fat deposition, fine facial hair, proximal muscle weakness
S.M. 37 years old with 85 lb weight gain over 7 years despite diet/exercise. Recent onset of Hypertension
Case 1: S.M.

- Evaluated by >20 health-care providers over span of seven years:
  - 24 Hour UFC: 181 mcg/day (range < 100)
  - Plasma ACTH 25 pg/mL
  - Adrenal CT- Negative
  - Pituitary MRI- Negative
  - She was told that her symptoms were due to depression and anxiety but referred to UCLA for further evaluation
Lesson: Cushing’s disease is not a radiographic diagnosis

Microadenomas  75 – 80%  (40% MRI-neg.)
Macroadenomas  20 – 25%

10 – 15% of the general population harbor incidental pituitary adenomas
Inferior Petrosal Sinus Sampling (IPSS)

- At experienced centers, sensitivity and specificity of 100%
- Lateralization in 70% of patients
- Correct interpretation requires that the patient be in a hypercortisolemic state:
  - Adrenosuppresive therapy
  - Cyclic Cushing’s Syndrome
- Other potential pitfall: Ectopic CRH syndrome
S.M.

- Low Dose Dex: 10 mcg/dL
- High Dose Dex: 2 mcg/dL

**IPSS with CRH**

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S.M.

- Underwent uncomplicated transnasal transphenoidal surgery
- Post-op serum cortisol = 1.7 ug/dl
- Post-op serum ACTH = 20 pg/ml
- Pathology: Pituitary adenoma
Case 2: S.S. Who has Cushing’s?
• At age 71, underwent abdominal CT scan for hematuria:
  – Left renal calculus
  – 1.7 cm adrenal nodule
• Past Medical History:
  – Kidney stones at age 41
  – At age 58, diagnosed with type 2 DM
    • No family history of diabetes
    • BMI at time of DM diagnosis 18.8 kg/square meter.
    • A1c controlled in 6% range with metformin. A1c progressively increased to 7.9% by age 72.
  – Osteoporosis T-score -2.6 at left femoral neck
  – Long standing history of bruising, worsened age 66 (had to cover entire body when playing tennis)
Lab work Up

- Fasting basal cortisol 19.1 ug/dL; ACTH 13 pg/mL
- UFC: 57, 32, 69 (normal <50 ug/day)
- 1 mg-Dex: Cortisol 18 ug/dL; ACTH 10 pg/mL; dexamethasone level 321 (range 180 -550 ng/dL)
- LNSC: 14 and 6.7 (normal < 4.3 nmol/L)
- Basal a.m. ACTH values: < 5, 8.1, 14.6 pg/mL
Treatment

- S.S. opted for Left laparoscopic adrenalectomy
- Adrenalectomy performed June 2015 (at age 73) without complications
- Placed on steroid replacement post-operatively
- Post-operatively, developed mild fatigue and dizziness
- At 4 week post-op visit, no improvement in cortisol levels:
  - AM cortisol: 20 mcg/dL (after withholding hydrocortisone x 24 hours)
  - Hydrocortisone discontinued
- Pathology: “macro-nodular hyperplasia with a predominant nodule”
Case 3: K.H.

History: 12 year old girl with 40 lb weight gain over 4 years despite caloric restriction, oligomenorrhea

Exam: Plethoric facies, acne, purple striae, central obesity

Growth: Height: 70 to 50 % tile  
          Weight: 30 to 95 % tile
Delayed Growth with Weight Gain—Girls

Stature-for-age and Weight-for-age percentiles

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</tbody>
</table>

Mother’s Stature
Father’s Stature

To Calculate BMI: Weight (kg) = Height (cm) x 703

*Stature: Height (cm) + (Length (cm) x 10,000)

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2005)
http://www.cdc.gov/growthcharts/
Case 3: K.H.

- Initially diagnosed as having PCOS and treated with OCPs
- UFC 397 mcg/day
- Plasma ACTH 91 pg/mL
- MRI indicative of 2 hypo-enhancing foci
- One foci was Rathke’s Cleft Cyst
- In remission after 4 transsphenoidal surgeries
Lesson: Spectrum of Clinical Presentation is Broad
Who should be screened?

- Patients with unusual features for age (e.g. osteoporosis, Hypertension)
- Patients with multiple and progressive features, particularly those more predictive of Cushing’s syndrome
- Children with decreasing height percentile and increasing weight
- Patient’s with adrenal incidentaloma
Prevalence of Cushing’s in certain high-risk populations

• 2-3% of patients with poorly controlled DM had surgically confirmed Cushing’s (Catargi, JCEM 2003)

• 1% of patients with newly diagnosed DM had surgically proven Cushing’s (Reimondo, Clin Endo, 2007)

• 5.8% of obese subjects referred to endocrine clinic with DM, HTN, and/or PCOS (Ness-Abramof, Obesity Research, 2002)

• 11% of older patients with osteoporosis and vertebral fracture in whom detailed testing was done for secondary causes (Chiodini, Ann Intern Med 2007)
Features that best discriminate Cushing’s syndrome

- Easy bruising
- Facial Plethora
- Proximal Myopathy
- Striae (especially if reddish purple and > 1cm wide)
Lessons

- Symptoms of PCOS overlap with Cushing’s
- Growth Chart is key in the diagnosis of Childhood Cushing’s Syndrome
- In adults, DEXA bone density scan may aid in distinguishing PCOS from Cushing’s syndrome.
Case 4: A.K.

- 37 year old woman with chief complaint of fatigue, body aches, hair loss and poor skin healing.
  - PMH: depression, eating disorder, hashimoto’s thyroiditis and vasculitis (treated with prednisone one year ago)
  - Meds: Plaquenil, Levothyroxine, Oral contraceptive pills
  - DEXA Scan: Osteoporosis
  - Exam: Thin, tearful woman. No stigmata of Cushing’s
Case 4: A.K.

- Serum cortisol 41 mcg/dL (range 8-19)
- ACTH 12 pg/mL (range 5-25)
- UFC 70 mcg/day (normal <50)
- Low dose Dex: 5.9 mcg/dL
- Normal Prolactin, TSH, and Free T4
- Free T3 and IGF-1 depressed
- Negative Pituitary and Adrenal MRI
Screening Tests

- UFC (at least 2 measurements)
- Late night salivary cortisol (2 samples)
- 1-mg overnight DST
- Longer low-dose DST (2 mg/day for 48 hours)
Pitfalls in Cushing’s Evaluation

• Drugs that elevate CBG will falsely elevate measurement of serum cortisol, which measures both CBG-bound and free hormone
  – Examples: Estrogen, Mitotane
  – False positive rates for overnight DST are seen in 50% of women taking OCPs
  – Stop estrogen containing drugs 6 weeks before testing

• Conversely, decreases in CBG are associated with decreased serum cortisol levels
  – Examples: Critical illness, nephrotic syndrome
Pitfalls in Cushing’s Evaluation

• Beware of drugs that alter dexamethasone metabolism
  – ↑ metabolism by induction of CYP 3A4:
    • Phenobarbital, phenytoin, carbamazepine, pimidone, rifampin
  – ↓ metabolism by inhibition of CYP 3A4:
    • Itraconazole, Ritonavir, Fluoxetine, Diltiazem

• Beware of drugs that increase UFC
  – Carbamazepine, Fenofibrate (HPLC), Licorice
Case 4: A.K.

- Serum cortisol normal after OCPs were withdrawn
- Mild elevation in UFC likely due to depression, anxiety and eating disorder
- Note: Endocrine findings in eating disorder
  - Elevated Cortisol
  - Low T3 and IGF-1
  - Low LH and FSH
  - Normal or mildly elevated Prolactin
Screening Tests

• Adrenal Incidentalomas
  – LNSC or 1-mg DST
  – Avoid 24 Hour UFC

• Cyclic Cushing’s
  – 24 Hour UFC for LNSC
  – Avoid 1-mg DST

• Renal Failure
  – 1-mg DST
  – Avoid 24 hour UFC
The patient knows best....
Case 5: J.I.

- 45 year old woman with a 40 lb weight gain over 4 years
  - Fatigue
  - Cognitive impairment
  - irregular menses
  - elevated fasting glucose
Case 5: J.I.
J.I. Lab Testing

- ACTH 31 pg/mL (6-50)
- Serum cortisol 10.6 mcg/dL
- UFC 25, 24, 14, 17, 22 mcg/d (range 4-50)
- 1 mg-DST: 0.5 mcg/dL
Case: J.I.

- Patient seen by 4 endocrinologists, 2 “pituitary endocrinologists”
  - Testing not supportive, but continue to monitor
- Patient: “I know I have cushing’s…”
- > 30 LNSC done over the span of 1 year
  - Several elevated
- MRI = negative
Case J.I.

• Trial of ketoconazole 200 mg BID
  – Stabilization of weight gain
  – Improved energy, mood and cognitive function

• IPSS (using DDAVP)
  – RIPS  Left IPS  IVC
  – 28   29   11  (baseline)
  – 180  258  19  (post DDAVP)
Case J.I.

• Pituitary Surgery X2
  – Post op cortisol 5 mcg/dL
  – 10 lab weight gain, but all symptoms recurred
• Medical therapy
  – Mifepristone (mild symptom improvement)
  – Pasereotide (mild symptom improvement)
  – Combined therapy (moderate improvement)
• Patient opted for bilateral adrenalectomy
POSTSURGICAL RECURRENT CUSHING DISEASE: CLINICAL BENEFIT OF EARLY INTERVENTION IN PATIENTS WITH NORMAL UFC

Review of MCW clinic records from July 2008 – July 2013

112 patients with CD undergoing primary therapy

- 47 excluded (insufficient data or LTFU)
- 65 with full data on initial outcome

15 with persistent disease after primary therapy

- 50 with initial remission
  - 15 with recurrence after initial remission
    - 3 with abnormal UFC
    - 12 with normal UFC
  - 35 in sustained remission
<table>
<thead>
<tr>
<th>Patient</th>
<th>Indications of recurrent CD</th>
<th>Treatment</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>Tumor growth, features of CS on physical exam</td>
<td>Repeat TSS</td>
<td>Post-op remission</td>
</tr>
<tr>
<td>2</td>
<td>DM, obesity, hypertension</td>
<td>Lost to follow-up</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>DM, obesity, hypertension, myopathy</td>
<td>Mifepristone and bilateral adrenalectomy</td>
<td>29-kg weight loss; improved blood pressure and muscle strength</td>
</tr>
<tr>
<td>4</td>
<td>DM, obesity, features of CS on physical exam</td>
<td>Mifepristone and bilateral adrenalectomy</td>
<td>1.5% improvement in HbA1c post-bilateral adrenalectomy</td>
</tr>
<tr>
<td>5</td>
<td>Weight gain and hypertension</td>
<td>Mifepristone</td>
<td>7.7-kg weight loss; improved mood and hypertension</td>
</tr>
<tr>
<td>6</td>
<td>Weight gain, hypertension, features of CS on physical exam</td>
<td>Cabergoline</td>
<td>Normalized ACTH and LNSC</td>
</tr>
<tr>
<td>7</td>
<td>Hypertension, decreased QoL, features of CS on physical exam</td>
<td>Mifepristone</td>
<td>Improved QoL and blood pressure</td>
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<tr>
<td>8</td>
<td>Myopathy, dyslipidemia</td>
<td>Repeat TSS</td>
<td>Post-op remission</td>
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<tr>
<td>9</td>
<td>Obesity, hypertension</td>
<td>Bilateral adrenalectomy</td>
<td>55-kg weight loss; hypertension resolved</td>
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<td>10</td>
<td>Weight gain, hypertension</td>
<td>Mifepristone</td>
<td>13-kg weight loss; hypertension resolved</td>
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<tr>
<td>11</td>
<td>DM, obesity, hypertension</td>
<td>Radiation and multiple repeat surgeries</td>
<td>Persistent disease</td>
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<tr>
<td>12</td>
<td>Hypertension, weight gain, features of CS on physical exam</td>
<td>Mifepristone therapy</td>
<td>HbA1c reduction from 6.1 to 5.7%</td>
</tr>
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</table>

**Patients with elevated UFC at time of recurrence**

<table>
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<tr>
<th>Patient</th>
<th>Indications of recurrent CD</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Weight gain, depression</td>
<td>Repeat TSS</td>
<td>Post-op remission</td>
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<tr>
<td>14</td>
<td>Hypertension, features of CS on physical exam</td>
<td>Cabergoline; switched to mifepristone</td>
<td>7-kg weight loss with mifepristone</td>
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<td>15</td>
<td>Weight gain, dyslipidemia, renal stones</td>
<td>Repeat TSS</td>
<td>No clear adenoma on repeat TSS. Post-op adrenal insufficiency and clinical remission</td>
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</table>

Abbreviations: ACTH = adrenocorticotrophic hormone; CD = Cushing disease; CS = Cushing syndrome; DM = diabetes mellitus; HbA1c = glycated hemoglobin; LNSC = late-night salivary cortisol; QoL = quality of life; TSS = transsphenoidal adenoma resection; UFC = urinary free cortisol.
Case 5: D.S.

• 34 year old woman with 30 lb weight gain, facial puffiness, and striae

• Evaluated by local University hospital and found to be hypertensive and placed on Diovan-HCTZ

• Patient entered symptoms into internet search engine and was routed to Discovery Channel episode on Cushing’s syndrome regarding S.M. (case 1)!!
Case 5: D.S.

- Serum Cortisol 34 mcg/dL (range 8-19)
- ACTH 146 pg/mL (range 6-48)
- 24 Hour UFC: 2,136 mcg/day (range 4-50)
- Salivary Cortisol 112 and 115 (range < 4)
- Serum Potassium 2.6 (after D/C of HCTZ)
- Estradiol – Undetectable
- HbA1c 6.8%
- Negative Pituitary MRI
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<tr>
<td>100</td>
<td>119</td>
<td>106</td>
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Whole Body PET-CT Scan

4 cm x 4 cm mass in the region of pancreatic tail
Octreotide Scan
Laparoscopic-assisted surgery

- Distal pancreatectomy
- Splenectomy
- Left adrenalectomy
- Wedge resection of liver
- Pathology: Pancreatic endocrine cancer (4.6 cm) with lymph node and liver metastases
- Post-op Upper GI bleed: Gastrin level >1576 pg/mL (range 0-100)
Assessing for remission and monitoring for recurrence
Case 4: B.C.

- 60 year old woman with rapid weight gain and easy bruising
- UFC 169 mcg/day (normal < 105)
- ACTH 57 pg/mL
- Salivary cortisol 5.3 and 7.1 nmol/L (normal < 4)
- Pituitary MRI Negative
## IPSS

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<tr>
<td>34</td>
<td>227</td>
<td>179</td>
<td>+30</td>
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</table>
Transsphenoidal surgery

- Suspicious area on the Left removed
  - Post-op Day 1 cortisol = 31 mcg/dL
  - Post-op Day 2 cortisol = 19 mcg/dL

- Patient taken back to surgery POD #2
- Left hemi-hypophysectomy done
  - Post-op Day 1 cortisol = 5 mcg/dL
  - Post-op Day 2 cortisol = 2 mcg/dL
CLINICAL REVIEW: Early Morning Cortisol Levels as a Predictor of Remission After Transsphenoidal Surgery for Cushing's Disease

Felice Esposito, Joshua R. Dusick, Pejman Cohan, Parham Mofakhar, David McArthur, Christina Wang, Ronald S. Swerdloff, and Daniel F. Kelly

Division of Neurosurgery (F.E., J.R.D., P.M., D.M., D.F.K.), Pituitary Tumor and Neuroendocrine Program (F.E., P.C., D.F.K.), and Division of Endocrinology (P.C.), University of California, Los Angeles (UCLA), School of Medicine, Los Angeles, California 90095; Department of Neurological Sciences (F.E.), Division of Neurosurgery, Università degli Studi di Napoli Federico II, 80131 Naples, Italy; UCLA Gonda Diabetes Center (P.C.), Los Angeles, California 90095; and Division of Endocrinology, Metabolism, and Nutrition (C.W., R.S.S.), Harbor-UCLA Medical Center, Torrance, California 90602

Introduction: We describe the use of serum cortisol and ACTH levels on postoperative d 1 and 2 as remission predictors after transsphenoidal surgery for Cushing's disease (CD).

Methods: Morning cortisol and ACTH levels were drawn daily after surgery; glucocorticoids were withheld until evidence of hypocortisolism. Early remission was defined retrospectively as a subnormal morning cortisol level ($\leq 140$ nmol/liter, $\leq 5 \mu g/dl$) on postoperative d 1 or 2 and sustained remission as subsequent eucortisolism.

Results: Of 40 consecutive adults with CD (mean age 39 yr), 80% achieved early remission. Of 39 patients with a minimum follow-up of 14 months (mean 39 months), 31 (79.5%) achieved sustained remission at a mean follow-up of 32 months, including 30 of 31 (97%) with early remission and one of eight (12%) without early remission ($P < 0.0001$). Sustained remission was achieved in 26 of 28 (93%) patients having their first operation, compared with five of 11 (45%) with a prior unsuccessful operation ($P < 0.001$). For the 32 patients in early remission vs. the eight in nonremission, mean fasting cortisol levels were 67.6 ± 33.0 (2.06 ± 1.2 μg/dl) vs. 691.1 ± 352.2 nmol/liter (22.9 ± 12.8 μg/dl) ($P < 0.0001$), and mean ACTH levels were 11.9 ± 6.5 vs. 64.1 ± 54.6 ng/liter ($P < 0.001$). Of 31 patients with sustained remission, 100% had subnormal morning cortisol levels, whereas 31% had subnormal ACTH levels ($P < 0.0001$).

Conclusions: Serum morning cortisol levels on postoperative d 1 and 2 without glucocorticoid replacement provide a safe, simple, and reliable measure of early remission for CD and are predictive of sustained remission. This method allows for consideration of a repeat operation during the same hospitalization in patients with persistent hypercortisolism. (J Clin Endocrinol Metab 81: 7-13, 2006)
# Patients

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<th>Characteristics</th>
<th>Value</th>
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<td>No. patients</td>
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<tr>
<td>Females</td>
<td>37 (93%)</td>
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<tr>
<td>Males</td>
<td>3 (7%)</td>
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<tr>
<td>Age</td>
<td>21-70 y (mean 39)</td>
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<tr>
<td>Microadenomas</td>
<td>23 (57.5%)</td>
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<tr>
<td>Macroadenomas</td>
<td>9 (22.5%)</td>
</tr>
<tr>
<td>Non-visible microadenoma</td>
<td>8 (20%)</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>11 (27.5%)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>14 - 65 months (mean 33)</td>
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# Remission Rate – Cushing’s Disease

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<tr>
<th>Tumor Size</th>
<th>Remission Rate</th>
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<tr>
<td>Microadenomas</td>
<td>21/23 (91%)</td>
</tr>
<tr>
<td>Macroadenomas</td>
<td>6/8 (75%)</td>
</tr>
<tr>
<td>Normal MRI*</td>
<td>4/8 (50%)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>31/39 (79.5%)</strong></td>
</tr>
</tbody>
</table>

- First-time surgery: 26/28 (93%)
- Re-operation: 5/11 (45%)

Mean follow-up 33 months (range 14 – 65 months)
Predictors of Remission

Tumor visible on MRI \( (p<0.05) \)
First-time surgery \( (p<0.05) \)

Of 31 patients with sustained remission
- Subnormal cortisol level in 100%
- Subnormal ACTH level in 31% \( (p<0.0001) \)
Timing of Remission

Of 32 patients with early remission:

- 15 (47%) on POD#1
- 17 (53%) on POD#2

-Time of surgery correlated with day of remission \( (p<0.05) \)
## Procedure Performed

<table>
<thead>
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<th>Procedure</th>
<th>No. subjects</th>
<th>Long-term remission</th>
<th>New pituitary failure</th>
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</thead>
<tbody>
<tr>
<td>Selective adenomectomy</td>
<td>30 (77%)</td>
<td>28/30 (93%)</td>
<td>0/31</td>
</tr>
<tr>
<td>Partial hypophysectomy</td>
<td>8 (20%)</td>
<td>4/8 (50%)</td>
<td>0/8</td>
</tr>
<tr>
<td>Total hypophysectomy</td>
<td>1 (2.5%)</td>
<td>0/1</td>
<td>1/1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>39</strong></td>
<td><strong>32/39 (82%)</strong></td>
<td><strong>1/39 (2.5%)</strong></td>
</tr>
</tbody>
</table>
Complications

Death (sepsis, multi-organ failure) 1
Carotid artery injury 1
CSF leak 1
Abdominal wound infection 1
New pituitary failure 1

TOTAL 5
Post-op A.M. Cortisol and ACTH nadir within 48 hrs of surgery

Cortisol p<0.0001
ACTH  p<0.0001

30 of 31 (97%) patients with A.M. cortisol ≤ 5 mcg/dl remain in remission
Post-op A.M. Cortisol and ACTH nadir within 48 hrs of surgery

Group I – remission
Group II – failure

Cortisol $p<0.0001$
ACTH $p<0.0001$

64 of 66 (97%) patients with A.M. cortisol $\leq 5$ mcg/dl remain in remission
Predicting Long-term Remission after Transsphenoidal Surgery for CD

- Early post-op serum cortisol in absence of glucocorticoids:
  - In our series, in the 32 patients achieving early remission, the average A.M. cortisol nadir was 2.05 ± 1.2 mcg/dL.
  - An A.M. cortisol level of ≤5 mcg/dL on post-operative day #1 or #2 was predictive of sustained remission in 97% of patients.
Advantages of Early Post-op Serum Cortisol Levels for Remission Criteria

• No provocative testing required
• Gives early and reliable answer about early remission, typically within 48 hrs of surgery
• Although patients with an early cortisol < 5 off w/o glucocorticoid replacement often develop symptoms of hypocortisolemia, manifestations of an adrenal crisis have not occurred.
• Allows early identification of patients with failed surgery who may be candidates for re-operation
• Longer term follow-up required to better assess this methodology
Cushing’s Disease – Management Protocol

• **Confirm diagnosis**

• **Surgery:**
  – Selective adenomectomy when possible
  – Partial hemihypophysectomy if no tumor found
  – Avoid total hypophysectomy

• **Post-op:**
  – No post-operative glucocorticoids
  – Monitor ACTH and cortisol Q12hrs for 48 hrs
  – Early mobilization

• **Long-term management:**
  – Wean steroid replacement over 6 -12 months
  – Regular assessment of 24 hr UF cortisol
Management of Recurrent Disease

• At age 19, began to develop acne, hair loss, fatigue
• At age 21, gained 50 lbs. in 3 months
• By age 23, her weight had increased from 120 to 205 lbs.
  • HTN, hyperlipidemia, IGT, depression, cognitive decline
Diagnostic Testing (2002)

- Serum cortisol 25 mcg/dL
- 24 Hour UFC: 160 mcg/day (range < 50)
- Plasma ACTH 64 pg/mL (range 5-27)
- Pituitary MRI- Possible 5 mm lesion
- IPSS: Central : Peripheral ACTH gradient
Transsphenoidal Surgery
(May 2002)

- Prolonged post-operative secondary adrenal insufficiency
  - Recovery of HPA axis in 2006-2007
  - Weight returned to baseline of 118 lbs.
- Hypothyroidism
- Low IGF-1
- Normal menses
October 2009

- Weight back up to 157 lbs.
- 24 Hour UFC: 64 mcg/day (<50)
- ACTH 51 pg/mL (5-27)
August 2011

- Weight up to 202 lbs.
- 24 Hour UFC: 168 mcg/day (<34)
- ACTH 67 pg/mL (<48)
- MRI: possible area of hypo-enhancement in right sella
Recurrence rate of Cushing’s disease after initial successful transsphenoidal surgery.

Patil, CG et al, JCEM 2008; 93(2):358-362
August 2011

- 24 Hour UFC: 168 mcg/day (<34)
- ACTH 67 pg/mL (<48)
- MRI: possible area of hypo-enhancement in right sella
Treatment Options

• Repeat Surgery
• Medical therapies
  – FDA approved (Mifepristone, Pasireotide)
  – Off-label (cabergoline, ketoconazole, metyrapone, mitotane, etomidate)
• Radiosurgery
• Bilateral adrenalectomy
TABLE 2. Potential preoperative and intraoperative predictors of remission after repeat transsphenoidal surgery for recurrent Cushing’s disease.

<table>
<thead>
<tr>
<th>Potential predictors of disease remission</th>
<th>No. of patients (n = 36)</th>
<th>No. of patients in remission after repeat TS surgery (remission rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic appearance on MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microadenoma</td>
<td>23</td>
<td>13 (56.5%)</td>
</tr>
<tr>
<td>Macroadenoma</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Negative MRI</td>
<td>10</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Extent of resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective adenomectomy</td>
<td>24</td>
<td>14 (58.3%)</td>
</tr>
<tr>
<td>Hemihypophysectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Subtotal hypophysectomy</td>
<td>6</td>
<td>4 (66.7%)</td>
</tr>
<tr>
<td>Total hypophysectomy</td>
<td>5</td>
<td>4 (80.0%)</td>
</tr>
<tr>
<td>Final pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive for ACTH-staining tumor</td>
<td>24</td>
<td>12 (50.0%)</td>
</tr>
<tr>
<td>Negative for ACTH-staining tumor</td>
<td>12</td>
<td>10 (83.3%)</td>
</tr>
<tr>
<td>Intraoperative identification of lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive identification of tumor</td>
<td>32</td>
<td>19 (59.5%)</td>
</tr>
<tr>
<td>Tissue suspicious for tumor</td>
<td>3</td>
<td>2 (66.7%)</td>
</tr>
<tr>
<td>No tumor seen intraoperatively</td>
<td>1</td>
<td>1 (100 %)</td>
</tr>
</tbody>
</table>

Note: TS, transsphenoidal; MRI, magnetic resonance imaging; ACTH, adrenocorticotropic hormone.
Repeat Transsphenoidal Surgery September 2011

• Immediate post-op cortisol < 1 mcg/dL
• Placed on corticosteroid replacement
• February 2012: Recovery of HPA axis
  – AM cortisol 9.6 mcg/dL
  – Hydrocortisone stopped
  – Minimal significant change in weight or other clinical improvement (weight 193 lbs.)
• December 2013: UFC 55 mcg/day (<50)
Off-label Medical Therapies

• Ketoconazole
  – 50% response rate
  – 23% escape rate

• Metyrapone
  – 40% response rate
  – 20% escape rate

• Cabergoline
  – 30% response rate
FDA-approved medical therapies

• Mifepristone
  – February 17, 2012

• Pasireotide
  – December 14, 2012
Medical therapy targets of the HPA axis

- SRL (Pasireotide) reduces ACTH/Cortisol and Tumor size.
- GR Antagonist (Mifepristone) increases ACTH/Cortisol and reduces Tumor size.

- Cortisol feedback inhibits ACTH secretion.
- GR binds to GRE, activating transcription.
- No dimerization inhibits GR activation.
- Active GR monomer promotes transcription.
- Dimerization enhances GR activation.
- Cytoplasmic activation is required for GR function.
MIFEPRISTONE: INDICATION

A cortisol receptor blocker indicated to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.
SEISMIC: 50 subjects, open label, 6 month study (Fleseriu, et al JCEM June 2012)

Participants screened (N=84)

Enrollment (n=50)

Screen failures (n=34)

ITT/Safety population

C-DM (N=29)
- Completers (n=20)
  - Withdrew (n=9)
    - Adverse event (n=2)
    - Death (n=1)
    - Withdrawn consent (n=4)
    - Other (n=2)

C-HT (N=21)
- Completers (n=14)
  - Withdrew (n=7)
    - Adverse event (n=5)
    - Death (n=1)
    - Withdrawn consent (n=1)
    - Other (n=0)
Baseline Characteristics (N=50)

- Cushing’s disease: 43
  - 42 had undergone previous pituitary surgery
  - 18 had prior pituitary radiation

- Ectopic Cushing’s syndrome: 4

- Adrenal cortical carcinoma: 3
Primary Endpoints

• Cushing’s + T2DM/IGT
  – Change in AUC for glucose on OGTT
  – Response: ≥ 25% decrease in AUC
    • Response rate: 60%

• Cushing’s + HTN
  – Change in DBP from baseline
  – Response: DBP decrease by ≥5 mm Hg
    • Response rate: 38%
(Fleseriu, et al JCEM June 2012)
Secondary Endpoints

- 5.7% mean reduction in weight
- Mean percent total body fat declined by 3.6%
- Waist circumference declined by 6.8 cm in women and 8.4 cm in men
(Fleseriu, et al JCEM June 2012)
Mifepristone: Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>% subjects (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>48</td>
</tr>
<tr>
<td>Fatigue</td>
<td>48</td>
</tr>
<tr>
<td>Headache</td>
<td>44</td>
</tr>
<tr>
<td>Endometrial hypertrophy</td>
<td>38</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>34</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>30</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20</td>
</tr>
</tbody>
</table>
SEISMIC: Extension Study
(Fleseriu, et al JCEM October 2014)

SEISMIC CD Patients Enrolled (n=43)

SEISMIC 24 Week Completers (n=31)

Withdrawals (12):
- Withdrew consent (n=5)
- Adverse event (n=6)
- Non-compliance (n=1)

SEISMIC LTE (n=27)

Not enrolled (4):
- Not eligible/non-compliance (n=1)
- Did not consent (n=2)
- Withdrew consent prior to dosing (n=1)
MRI Findings

Nonvisible (N= 20)

- Progressed (1)
- Stable (19)
MRI Findings

Microadenoma \( N = 9 \)

- Progressed \( (0) \)
- Stable \( (8) \)
- Regressed \( (1) \)
MRI Findings

Macroadenoma (N= 7)

- Progressed (3)
- Stable (3)
- Regressed (1)
PASIREOTIDE: INDICATION

A somatostatin analog indicated for the treatment of adult patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative.
Phase III Study Design
A. Colao et al NEJM 2012

• 12 Month Randomized Study
• Arm 1: Pasireotide 0.6 mg sc bid
  – N=82
• Arm 2: Pasireotide 0.9 mg sc bid
  – N=80
Mean Change in Urinary Free Cortisol Levels from Baseline to Month 12

Patients with Normalized Levels at Month 6

<table>
<thead>
<tr>
<th></th>
<th>0.6 mg bid</th>
<th>0.9 mg bid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UFC Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Responders</td>
<td>15%¹</td>
<td>26%²</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>82</td>
<td>80</td>
</tr>
</tbody>
</table>

¹95% CI 22%
²95% CI 36%

Changes in Signs and Symptoms of Cushing's Disease and UFC Levels

### Pasireotide: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>% Subjects (N=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>58</td>
</tr>
<tr>
<td>Nausea</td>
<td>52</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>40</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>30</td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>17</td>
</tr>
<tr>
<td>HbA1c increased</td>
<td>11</td>
</tr>
</tbody>
</table>
Case Presentation

- Mifepristone started at 300 mg/day
- No significant clinical response until dose escalated 1500 mg/day
  - 20 lb weight reduction
  - amenorrhea
Medical Therapies: Under Investigation

Osilodrostat (LCI699)
Levoketoconazole (COR-003)
R-roscovitine
Retinoic Acid
Sites of Action of Novel Medical Therapies

R-roscovitine CYC202
- Lower ACTH transcription
- Lower ACTH secretion

COR-003
- Cholesterol
- CYP17A1
- 17-OH-Pregnenolone
- 17-OH-Progesterone
- Deoxycorticosterone
- CYP11B1
- Cortisol

LCI699
- Retinoic Acid
- Corticotrophe cell nucleus
- Cell Cycle Arrest

Adrenal cortex

COR-003

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Questions