Disclosure

- Chiasma, Cortendo, Novartis, Pfizer
  - Principal investigator: Research funding to OHSU
  - Scientific consulting fee
Do endocrinologists need to be consulted preoperatively for pituitary and adrenal tumors?

**Pituitary**
- Does the patient need surgery from an endocrine standpoint?
- How long should patients be monitored/kept inpatient?
- How and when do we re-evaluate the patient postoperatively?
- Do we have any data (randomized trials) for how to best manage patients?

**Adrenal**
- Is this a secretory tumor?
- When do we need to find out if it is inpatient or outpatient?
- Will need removal from an endocrine point of view?
Case

CC: 54 y old with headache + altered mental status

HPI:
• Missed work which was unusual for him.
• He was called into work where he became increasingly confused and disoriented while also complaining of a headache.
• As part of his work up in ED, a CT revealed a large sellar and suprasellar mass and he was transferred to our hospital for further workup and management.

ROS: Headache, confusion, somnolence, vision loss?
General Appearance: Obese male, lying in bed, awakens to voice briefly holding bridge of nose with eyes closed.

HEENT: MMM, mild conjunctival injection, no moon facies, no facial plethora.

Neck: +dorso-cervical fat pad enlargement, no supraclavicular fat pad enlargement.

Abdominal: soft, NT, +BS, no violaceous striae.

Skin: no acne, skin not oily, did not have multiple skin tags.

Neurologic: bilateral eyelid apraxia, upgaze deficit, no facial droop, able to move all 4 extremities spontaneously against gravity, somnolent, oriented to self and year.
Imaging

MRI with contrast homogenously $5.8 \times 3.4 \times 2.5$ cm sellar, supra sellar mass extending into the third ventricle and interpeduncular cistern causing secondary obstructive hydrocephalus. The right cavernous carotid is encased.
Hormonal work-up

- TSH 0.64 mLU/l
- Free T4: 0.7 (0.6-1.2)
- Prolactin: 99* 
- ACTH: 22
- Cortisol: 9.4 ug/dL
- FSH<1, LH<1
- Testosterone: 22
- IGF-1 152 ng/ML (68-245ng/ML)
What is next?

• Patient underwent transphenoidal pituitary surgery
• Pathology
  – Sections show fragments of anterior pituitary tissue with disrupted acinar architecture (highlighted by reticulin stain) and involvement by sheets of relatively monomorphic adenoma cells which strongly express prolactin.
  – Adrenocorticotrophic Hormone Negative
    Human Growth Hormone Negative
    Prolactin Positive
    Cyto-Keratin CAM 5.2 Positive focal
    Somatostatin Receptor 2A Positive
    Ki67 % Positive 5%
    p53 Negative
    Negative control slide for IHC stain Negative
    SF-1 Positive focal
What Now?

What is the diagnosis?

Reminder:

PRL 99 with dilution
SF-1 positive
Cell Lineage specific transcription factors

- Pit-1
- T-pit
- SF-1
- ER

![Diagram of cell lineage specific transcription factors and their interactions](image)
Initial evaluation for large tumors

• Imaging - ideally pituitary dedicated MRI

• Visual field testing (if mass abuts/compresses optic nerve)

• Evaluate HPA axis

• Check for clinical and biochemical signs of hormone excess
Evaluate for hormonal secretion

- Prolactin
- ACTH/ Cortisol
- IGF-1
- TSH/FT4
- LH/FSH-estrogen/testosterone

- If prolactinoma-medical therapy > surgical therapy.
- Acromegaly and Cushing's disease at increased risk for cardiovascular complications.
Adrenal insufficiency

- Check AM cortisol +/- ACTH
- If results equivocal or clinical suspicion, cosyntropin stimulation test
- Goal: treatment to prevent adrenal crisis, particularly if patient is going for surgery
TSH

Evaluate for central hypothyroidism & central hyperthyroidism

• Check Free T4 + TSH

• Central hyperthyroidism very rare

• TSH not reliable even if normal or elevated

• Exact cut-off for repletion varies
  – Replacement can prevent hyponatremia, cardiac complications and postoperative ileus
ADH

DI → inadequate AVP response to serum osmolality

- More common in suprasellar lesions
  - Craniopharyngyomas (81%-96% post op)

Adipsic DI - rare entity

- Craniopharyngiomas accounts for 13-30% of cases
  - Particularly in tumors greater than 3.5 cm or causing hydrocephalus
- Other causes include other suprasellar lesions, congenital, infection, aneurism clipping, toluene exposure
- Occurs when patients have inadequate thirst response for rising serum osmolality
- High morbidity and mortality
  - Central sleep apnea
  - Excess somnolence
  - DVT
  - AKI
GH /LH-FSH axes

- IGF-1 should be checked in all tumors in my opinion.
- LH, FSH can wait if patient will undergo surgery as they will need re-evaluation post operatively.
- No current role for alpha subunit.
- Most “silent adenomas” are gonadotroph adenomas.
Prolactin

- Typically degree of *prolactin elevation* correlates with *size of tumor*
Other giant tumor

Fleseriu et al, J Neuroonc, 2006
Hook effect

- Prolactin levels in giant prolactinomas can be misleading
- Essentially antigen-(prolactin) interferes with assay by preventing complex formation with capture antibody and signal antibody

- Dilution is required to lower prolactin levels enough to enable antibody complex formation

- Mild prolactin elevation in range of stalk effect can be misleading in giant adenomas
  - verifying serial dilutions is key

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MRI after surgery and Cabergoline

Fleseriu et al, J Neuroonc, 2006
## Early postoperative complications

### Surgical
- **Sellar hematoma** → visual loss
- Diplopia
- Headache
- CSF leak
- ICA injury
- Hydrocephalus
- Epistaxis
- Infection
  - Meningitis
  - Sinusitis
  - Abscess

### Endocrine
- DI
- SIADH
- Adrenal insufficiency
Early Postoperative Management

- Serial visual field assessments
- Serial neurologic exams
- Imaging if new neurologic deficit or suspected CSF leak
- Strict ins and outs
- Monitor serum sodium, urine SPG (less than 1.005) or osm
- UOP > 250 ml/h x 2-3 hours
- DDAVP if indicated?
- AM Cortisol*
- Serum sodium in 5-7 days post op
Evaluation of remission in functional adenomas

- Moderately predictive of early and long term remission.

**POD 1**
- Fasting AM GH less than 1 or 2 ng/ml
- Prolactin level less than 10 ng/mL
- Cortisol *

- **CD**
  - Multiple protocols to evaluate “cure” Cushing's
  - Steroids held and serial measurements of post op cortisol
  - Particularly important as they may either need further treatment or are adrenally insufficient
Electrolyte abnormalities following transphenoidal pituitary surgery

Prospective study- N=57

• Day 0-14
• 75% of patients had some sodium abnormality
• 38.5% Isolated DI
• 21% isolated Hyponatremia
• 15.7% had combined DI + Hyponatremia
• 8.7% of patients required DDAVP for more than 3 months
• Pituitary manipulation most strongly correlated with risk of DI

How long to keep the patient in the hospital?

For DI and SIADH monitoring?
Peak incidence DI: 24-48 hours.
Typically do not keep in hospital to see if they develop SIADH.

To evaluate for remission:
Cushing's
- We hold steroids and then check cortisol q6 hours x 4.
Acromegaly
- Check am GH POD 1 & 2.
Inpatient multidisciplinary pituitary team

- Retrospective study comparing outcomes before and after implementation of a multidisciplinary team and protocol
- N:214, 113 before and 101 after protocol
- Median length of stay decreased from 3 to 2 days (P<0.01)
- No difference in rate of DI or SIADH or other complications
Glucocorticoids for “non Cushing's” patients

- AM cortisol may be helpful in determining central adrenal insufficiency post op.
- CST unreliable for at least two weeks
- Multiple different approaches including
  - Empiric stress dose steroids before surgery + discharge on physiologic replacement, evaluate in 6 weeks
  - Steroids if post op am cortisol less than 10-15 mcg/dl
  - Steroid sparing: no perioperative steroids and careful post operative monitoring for AI
6 + 12 weeks postoperatively

• Evaluate HPA axis at week 6 + 12
  – Cosyntropin stimulation test

• Reevaluation for other pituitary axes

• Initiate repletion for new hormonal deficits if any

• Post operative MRI at week 12 → “new baseline”
Long term follow up

• Depends on the tumor type

• Periodic MRI (annually for 3-5 years)

• Monitoring for hormone excess

• Periodic HPA axis evaluation (at least annually)
  – Recovery is higher than previously thought, especially in acromegaly patients
Preoperative Hormonal Evaluation:
- Adrenal
- Prolactin
- Thyroid
- GH
- Gonadotroph

Replace thyroid and adrenal hormones if insufficiency detected preoperatively

Transsphenoidal Surgery
Perioperative stress dose steroids if indicated

Early Inpatient Monitoring
- 1 week:
  - General status, sodium, cortisol
- 6 week:
  - General status, Adrenal, thyroid, GH, Prolactin
- 12 week:
  - General status, Adrenal, thyroid, gonad, GH, Prolactin as clinically indicated
  - MRI – Baseline post op image

Outpatient Follow up

Early outpatient Assessment
- 1 week:
  - General status, sodium, cortisol
- 6 week:
  - General status, Adrenal, thyroid, GH, Prolactin
- 12 week:
  - General status, Adrenal, thyroid, gonad, GH, Prolactin as clinically indicated
  - MRI – Baseline post op image

Long Term Follow up
- Hormonal status evaluation annually or as dictated by clinical state
- Assessment for tumor recurrence
- Assessment for biochemical remission

Adapted from: AACE Neuroendocrine and Pituitary Scientific Committee. Endocr Pract. 2015
MOC question

• A 29-year-old woman is known to have partial hypopituitarism (on replacement with Hydrocortisone 15 mg daily and Levothyroxine 100 mcg daily) after surgery for a 2.4 cm pituitary adenoma several years ago. Residual tumor significantly increased in the last 2 years and a second pituitary surgery is planned. You see her in the endocrinology clinic the week of her surgery and give recommendations to the patient and the on-call endocrinologist who will manage the patient in the hospital.
Which of the following statements is TRUE?

1. Change her glucocorticoid regimen now from Hydrocortisone to Prednisone to better prepare her for surgery
2. Increase her daily hydrocortisone from 15 mg to 20 mg daily a week before surgery to avoid use of stress dose perioperatively
3. Stop levothyroxine in the hospital, it won't get absorbed anyway and recheck TSH in the first 3-4 weeks after surgery
4. Fixed doses of DDAVP should be prescheduled in the immediate postoperative period as this is her second pituitary surgery
5. She will need retesting of all pituitary axes starting at 6 weeks after pituitary surgery and then periodically to monitor the development or resolution of pituitary deficiencies.

Adrenal mass-inpatient

- Is the mass functional?
- Physical signs or symptoms of hyperfunction?
- Biochemical work-up:
  - Screen for pheocromocytoma
  - Potassium/aldosterone/renin
  - Cushing’s
- Is the mass malignant?
- Bilaterality of disease?
- Monitoring for hormone excess after surgery
Imaging
Imaging
Biochemical Workup

• Adrenal Incidentaloma
  – Pheochromocytoma: 24 hour urine metanephrines
  – Primary Hyperaldosteronism: If hypertensive (with or without hypokalemia) do PAC/PRA ratio
  – Cushing’s Syndrome: Screen for excess cortisol production

If not urgent, preferred work-up as outpatient

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Value</th>
<th>ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>METANEPHRINES (0.00 - 0.49 nmol/L)</td>
<td>19.10</td>
<td>38x ULN</td>
</tr>
<tr>
<td>NORMETANEPHRINES (0.00 - 0.89 nmol/L)</td>
<td>&gt;50</td>
<td>56x ULN</td>
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<tr>
<td>EPINEPHRINE CONCENTRATION (10 - 200 pg/mL)</td>
<td>7,180</td>
<td>36xULN</td>
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<tr>
<td>NOREPINEPHRINE (80 - 520 pg/mL)</td>
<td>39,520</td>
<td>76x ULN</td>
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<tr>
<td>DOPAMINE (0 - 20 pg/mL)</td>
<td>1,480</td>
<td>74x ULN</td>
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<table>
<thead>
<tr>
<th>Urine</th>
<th>Value</th>
<th>ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>METANE/CREA RATIO UNL</td>
<td>0 - 300 ug/g CRT</td>
<td>13,488</td>
</tr>
<tr>
<td>NORMETANEPHRINE UR 109 - 393 ug/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NORMETAN/CRE RATIO 0 - 400 ug/g CRT</td>
<td>16,415</td>
<td>41xULN</td>
</tr>
</tbody>
</table>
Evaluation of an adrenal incidentaloma

- Size
  - > 4 cm → Surgery after pheochromocytoma evaluation*
  - < 4 cm
    - CT/MRI characteristics
      - malignant
        - < -20 HU: myelolipoma
          - F/U if large
        - benign
          - Hormonal eval
      - Urine catecholamines
        - Plasma free metanephrine
          - If clearly abnormal, surgery
      - If hypertensive,
        - Renin:Aldo
          - If >20, confirm with other test then surgery
        - If normal, 1 additional F/U only
  - If normal, follow-up @ 1 yr
    - Exclude pheochromocytoma
    - Exclude hypercortisolism
    - (no eval for aldosteronism)
    - Image for mass increase
      - (obtain at 6 mo if worrisome)
        - Surgery if abnormal
        - If normal, 1 additional F/U only

* Dex suppression
  - LN salivary cortisol
  - UFC
    - (consider DHEAS, ACTH)
    - If clearly abnormal and symptomatic, surgery
## Preoperative treatment in pheocromocytoma

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Example/dose</th>
<th>Mechanism</th>
<th>Target</th>
<th>Benefit</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha blocker</td>
<td>Phenoxybenzamine— start 10 mg bid—</td>
<td>Alpha 1-adrenergic blockade leading to vasodilation</td>
<td>Starting 10–14 days before surgery</td>
<td>Mainstay of therapy Normalizes BP Aids expand intravascular volume</td>
<td>Postural hypotension</td>
</tr>
<tr>
<td></td>
<td>start 10 mg bid—</td>
<td></td>
<td>Titrate till achieve normal BP w/mild orthostasis</td>
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<td></td>
<td>Usual dose 1 mg/kg/day</td>
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<tr>
<td></td>
<td>Prazosin 2–5 mg</td>
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<tr>
<td></td>
<td>Terazosin 2–8 mg</td>
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</tr>
<tr>
<td></td>
<td>Doxazosin 2–8 mg</td>
<td></td>
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</tr>
<tr>
<td>Beta blocker</td>
<td>Propranolol 10 mg Q6 h</td>
<td>Beta-adrenergic blockade</td>
<td>Start at low dose e.g., propranolol 10 mg Q6 and increase as tolerated to target HR 60–80</td>
<td>Helps target BP and HR control</td>
<td>Only to be used after patient is on maximal dose of alpha blocker Use cautiously in patients with cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Atenolol 25–50 mg/day</td>
<td></td>
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<tr>
<td>Calcium channel</td>
<td>Nicardipine SR 30 mg bid starting dose</td>
<td>Reduction of catecholamine-mediated calcium influx in vascular smooth muscle</td>
<td></td>
<td></td>
<td>Augments BP control when other agents inadequate or intolerant side effects of alpha blockers</td>
</tr>
<tr>
<td>blocker</td>
<td>Nifedipine 30 mg/day starting dose, titrate to 60 mg/day</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Amlodipine 5–10 mg/day</td>
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</tr>
<tr>
<td>Catecholamine synthesis inhibitors</td>
<td>Metyrosine 250 mg q6 h → titrate over days to 1000 mg q6 h</td>
<td>Competitively inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis</td>
<td>Normotension</td>
<td>Used in metastatic disease adjunctive to other medications or for intolerance to other medical regimens</td>
<td>Significant side effects: sedation, depression, diarrhea, anxiety, nightmares, crystalluria and urolithiasis, galactorrhea, and extrapyramidal signs</td>
</tr>
</tbody>
</table>
Pheochromocytoma

Goals for inpatient treatment: Roizen criteria

- No in-hospital blood pressure >160/90 mmHg for 24 h prior to surgery
- No orthostatic hypotension with blood pressure <80/45 mmHg
- No ST or T wave changes for 1 week prior to surgery
- No more than five premature ventricular contractions per minute
Pheocromocytoma

• ~25-40% of otherwise sporadic PHEO-PGL now attributed to a **known genetic cause**.

• Most patients don’t have clinical features to inform genetic testing, therefore, inclusive (unbiased) gene panels are reccomended (for ex whole exome sequencing).

• If VHL, NF1, MEN2 diagnosed on basis of history or clinical manifestations, direct testing of the suspected gene is recommended.

**Strong consideration for an individualized surveillance plan- genetic counseling and testing**
Cushing’s syndrome

- Low Dose DST is best test to assess adrenal autonomy
- 1mg Dexamethasone @ 2300, check cortisol @ 0800 AM Cortisol

Cutoff values

- Endocrine Society: >1.8ug/dL
  - Sensitivity >95%
  - Specificity 80%

Young, WF. The Incidentally Discovered Adrenal Mass. NEJM 356(6); 2007, 601-610.
Low dose Dex

• Consider cortisol-binding globulin
  – Estrogen ↑s CBG → false + results if patient is on OCP
  – Low albumin (ill patient, nephrotic syndrome) ↓s CBG → Falsely low cortisol levels

• Consider altered clearance of dexamethasone
  – Antiseizure medications, alcohol & rifampicin induce hepatic clearance of dex
  – Renal/liver failure decrease clearance of dex
  – Check dexamethasone level at same time as cortisol level
    • >5.6nmol/liter (0.22ug/dL) considered appropriate for suppression

Preoperative medical treatment in severe CS

Medical Therapy

Adrenals

Adrenal steroidogenesis inhibitors
- Ketoconazole
- Metyrapone
- Mitotane
- Etomidate

Levoketoconazole (in clinical trials)

Peripheral tissue

Glucocorticoid receptor blocker
- Mifepristone

Mifepristone

GR (antagonist)

Agonist

Intracellular Nucleus

GR antagonist bonds with GR, the complex moves to the nucleus and bonds with GRE to inhibit transcription.

# Adrenal steroidogenesis inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pros</th>
<th>Additional comments</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Rapid action</td>
<td>Twice/thrice-daily dosing May be preferred in women</td>
<td><strong>Side effects:</strong> GI, male hypogonadism</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>New FDA warning LFTs (rare, serious)</td>
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<td></td>
<td></td>
<td></td>
<td>Gastric acidity required for absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Many drug–drug interactions</td>
</tr>
<tr>
<td>Metyrapone</td>
<td>Rapid action</td>
<td>Four-times-daily dosing Pregnancy? (not approved)</td>
<td><strong>Side effects:</strong> GI, hirsutism, hypertension, hypokalemia ‘Escape’?</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Beneficial in adrenal cancer</td>
<td>Avoid in women desiring pregnancy within 5 years</td>
<td><strong>Side effects:</strong> GI, neurologic, teratogenic, adrenolytic Delayed efficacy</td>
</tr>
<tr>
<td>Etomidate</td>
<td>Intravenous</td>
<td></td>
<td>Intensive ICU monitoring</td>
</tr>
</tbody>
</table>

Medical therapy before adrenalectomy in CS

- 11 patients
- Mitotane 3.0–5.0 g
  + Metyrapone 3.0–4.5 g
  + Ketoconazole 400–1200 mg daily dose

- Side effects: GI, rise in cholesterol, γGT
Time to recovery adrenal function after curative surgery for CS

- Retrospective analysis
- 91 patients with CS, 54 with CD
- Mean follow up time 8 years
- Time to recovery
  - 0.6 years in ectopic Cushing's syndrome
  - 1.4 years in Cushing's disease
  - 2.5 years in adrenal Cushing's syndrome

- Patients with CD recover adrenal function after surgical “cure” quicker than adrenal CS

- Average recovery of adrenal function in CS in recent study was 11.5 months
Primary hyperaldosteronism and subclinical Cushing’s syndrome

- Cortisol co-secretion may appear in PA
- First studies: prevalence of subclinical Cushing’s 12-21%
- More studies are needed to evaluate prevalence
- *Concern for potential misinterpreting* of the adrenal vein sampling
  - Cosecretion of cortisol → can raise cortisol levels in the adrenal vein draining the APA → loss of lateralization (and a lost opportunity to offer potentially curative surgery) or give the impression that cannulation had failed on the contralateral side
- Risk of adrenal insufficiency after surgery if a diagnosis of CS is not entertained preop
Conclusion

Multidisciplinary teams comprising many specialties are instrumental in improving outcomes for patients with pituitary and adrenal tumors.

Future work is needed to create multicenter databases, especially in US to accumulate long-term data in rare disorders.
Thank you!

References attached
References


References

- Glowniak JVLoriaux DL A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery 1997;121123-129
- Primary Aldosteronism – Endocrine society guidelines 2008
- Huiras CMPehling GBCaplan RH Adrenal insufficiency after removal of apparently nonfunctioning adrenal adenomas. JAMA 1989;261894-898 Qi XP et al
References

• Stowasser M. Update in primary aldosteronism. J Clin Endocrinol Metab. 2015 Jan;100(1):1-10.
• Lenders JWPacak KWalther MM et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287 (11) 1427-1434
• Invited Commentary | October 2015 Nonoperative Management of Bilateral Adrenal IncidentalomasThe Value of Restraint, Linwah Yip et al
References

- Cardiovascular Manifestations of phaeochromocytoma