Pituitary and Adrenal “Perioperative” Endocrinology

Maria Fleseriu, MD, FACE
Professor, Director Northwest Pituitary Center
Oregon Health Science University

Disclosure

- Chiasma, Cortendo, Ipsen, 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?
Case continued

BP 118/65 | Pulse 64 | Temp 36.8 °C (98.2 °F) | RR 12 | Ht 1.803 m (5’11") | Wt 94.5 kg (208 lb 5.4 oz) | SpO2 96% | BMI 29.07 kg/(m^2)

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 x 3.4 x 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)
- GH 1.57 (<4.99 ng/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.
  - Adrenocorticotropic 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 mammalian neuroendocrine cell lineage determination]

Fig. 1. Model for development of human anterior pituitary cell lineage determination by a temporally controlled cascade of transcription factors. Trophectodermal cells are depleted with transcription factors known to determine cell-specific hormone or lineage gene expression. Adapted with permission from S. Ménard, Cell Tissue Res. 373 (2008) 383–408. doi:10.1007/s00441-008-0490-5.
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
- GH/ 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.
Evaluate for hormonal deficiencies

**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 $\Rightarrow$ inadequate AVP response to serum osmolality
- More common in suprasellar lesions
  - Craniopharyngiomas (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 osom
- 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

Smith TP et al. (2007) Technology Insight: measuring prolactin in clinical samples
Nat Clin Pract Endocrinol Metab 3: 279–289

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 osom
- 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 steroid and then check cortisol q6 hours x 4
- Acromegaly
  - Check am GH POD 1 and 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

Early Inpatient Monitoring

Neurologic status
Diabetes insipidus
SIADH

Replace thyroid and adrenal hormones if insufficiency detected preoperatively

Transsphenoidal Surgery
Perioperative stress dose steroids if indicated

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 Woodmansee WJ et al; AACE Neuroendocrine and Pituitary Scientific Committee. Endocr Pract. 2015
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
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**
Chromogranin relevance in neuroendocrine tumors

**KEY POINTS**

- Chromogranin A is a secretory marker and thus, captures only one aspect of NET behavior (monoanlyte).
- The metrics and monoanalyste character of the CgA assay, render it of limited utility as a NET biomarker since it does not measure tumor behavior, predict metastasis, or assess efficacy of treatment.
- CgA assay limitations include low reproducibility, poor sensitivity, modest specificity, and no standard.
- Overexpressed in other diseases, for example, colon cancer, cardiovascular disease, renal failure, and elevation by common medications, for example, proton pump inhibitors (PPIs) are confounding issues for measurement.
- Chromogranin A has been superseded by assay strategies that encompass measurement of multiple circulating tumor products, for example, transcripts.

DOI: 10.1097/MED.0000000000000215
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 <90/45 mmHg
- No ST or T wave changes for 1 week prior to surgery
- No more than five premature ventricular contractions per minute

Preoperative treatment in pheochromocytoma

<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—usual dose 1 mg/kg/day</td>
<td>Alpha 1-adrenergic blockade leading to vasoconstriction</td>
<td>Starting 10-14 days before surgery</td>
<td>Maintains BP, normalizes BP, reduces output</td>
<td>Proximal hypertension, hyponatraemia</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>Propranolol 10 mg Q8h</td>
<td>Alpha- and beta-adrenergic blockade</td>
<td>Start at low dose e.g., propranolol 10 mg Q6h increase as tolerated to target HR 60-80</td>
<td>Helps target BP and HR control</td>
<td>Only use if patient is on maximal dose of alpha blocker</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>Nicardipine SR 30 mg bid starting dose</td>
<td>Reduction of catecholamine-mediated calcium influx in vascular smooth muscles</td>
<td>Normalisation</td>
<td>Can be used as monotherapy if intolerant to other agents, beneficial in cardiomyopathy or coronary vasospasm</td>
<td>Augments BP control when other agents inadequate or intolerant side effects of alpha blockers</td>
</tr>
<tr>
<td>Catecholamine synthesis inhibitors</td>
<td>Metyrosine 250 mg q6h, max 1000 mg q6h</td>
<td>Competitively inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis</td>
<td>Normalisation</td>
<td>Used in metastatic disease adj. to other medications or for intolerance to other medical regimens</td>
<td>Significant side effects: sedation, depression, diarrhoea, anxiety, nightmares, crystals and urikemia, galactorrhoea, and extrapyramidal signs</td>
</tr>
</tbody>
</table>
**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 recommended (for example, 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%

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

Medical Therapy

Preoperative medical treatment in severe CS

- Adrenal steroidsogenesis inhibitors
  - Ketoconazole
  - Metyrapone
  - Mitotane
  - Etomidate
  - Levo-ketoconazole

- Glucocorticoid receptor blocker
  - Mifepristone

## 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</td>
<td>Side effects: GI, male hypogonadism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be preferred in women</td>
<td>New FDA warning LFTs (rare, serious)</td>
</tr>
<tr>
<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</td>
<td>Side effects: GI, hirsutism, hypogonadism, hypertension, hypokalemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy? (not approved)</td>
<td>‘Escape’</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Beneficial in adrenal cancer</td>
<td>Avoid in women desiring pregnancy within 5 years</td>
<td>Side effects: 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

Kamenicky et al. J Clin Endocrinol Metab. 2011 Sep;96(9):2796-804
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

Berr, J Clin Endocrinol Metab, April 2015

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
  - Co-secretion 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
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
• Levy A Perioperative steroidcover. Lancet 1996;347846-847
• 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
• Stowasser M. Update in primary aldosteronism. J Clin Endocrinol Metab. 2015 Jan;100(1):1-10.
References

- Invited Commentary | October 2015 Nonoperative Management of Bilateral Adrenal IncidentalomasThe Value of Restraint, Linwah Yip et al
- Cardiovascular Manifestations of pheochromocytoma