Endocrine Board Review
Pituitary and Adrenal Disorders

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Disclosures
- Principal Investigator in research studies/trials that take place at Emory University sponsored by Ipsen, Novartis and Chiasma
- Consultant (Advisory Board) for Ipsen, Novartis, Chiasma and Ionis

Objectives
- Recognize clinical, laboratory, radiological and therapeutic implications of pituitary adenomas
- Recognize clinical presentation and management of adrenal tumors and adrenal insufficiency

The Pituitary Gland
Adapted from Frohman, Endocrinology and Metabolism, ed. Felig, 1997

Pituitary Masses
- Pituitary adenomas
- Other CNS tumors
  - Craniopharyngioma
  - Germinoma
  - Teratoma
  - Meningioma
  - Glioma
- Tumors of the clivus
  - Sarcoma
  - Chordoma
- Metastases to the pituitary
  - Breast Ca
  - Lung Ca
- Granulomatous diseases
- Lymphocytic hypophysitis
- Pituitary Hyperplasia
  - Severe pr.
  - Hypothyroidism
  - Pregnancy
Pituitary adenomas

- High prevalence: 20% at autopsy, 10-15% by imaging
- Hormone production classification:
  - Non-functional
  - Functional (excess hormones)
- No gender prevalence except
  - Cushing’s disease and prolactinoma - more common in women

Immunohistochemistry

- PRL 30%
- Null cell 25%
- FSH, LH 10%
- GH 15%
- GH/PRL 7%
- ACTH 10%
- TSH 1%
- Other 2%

Size matters

- Microadenoma (< 1 cm)

Tumor Mass Effects

- Optic chiasm:
  - Visual field defects
- Cranial nVIII, IV, VI
  - Ophthalmoplegia
- Headaches
- Hypopituitarism
- Stalk effect:
  - High PRL
- Rarer:
  - Papilledema
  - Hydrocephalus
  - CSF rhinorrhea
  - Seizures

MRI pituitary:
- Macroadenoma
- Pituitary Stalk Deviation

Q1

A 31 y.o. F presents w/ amenorrhea which resolved w/ OCP. Two yrs ago, she began to notice a white discharge from her nipples which is now spontaneous.
Meds: sertraline for anxiety disorder.
Exam: BP 110/65, HR 68, Wt 60 kg, expressible galactorrhea.
Labs: TSH=0.58 mIU/l, T4 8.4 mcg/dl, PRL=600 ng/ml (nl 2-18).

Q1

Which of the following statements indicates the best course of action:

1. Continue tx w/ OCP for bone protection
2. Repeat PRL after stopping sertraline
3. Start tx w/ dopamine agonists
4. Refer to neurosurgery since this is a macroadenoma
4. Refer for gamma knife radiotherapy
Q1 - Answer
Which of the following statements reflects the best course of action:

1. Continue tx w/ OCP for bone protection
2. Repeat PRL after stopping sertraline
3. Start tx w/ dopamine (DA) agonists
4. Refer to neurosurgery for transsphenoidal adenoma resection since this is a macroadenoma
4. Refer for gamma knife radiotherapy

Causes of Hyperprolactinemia

1. Prolactinoma
2. Pharmacologic: phenothiazines, butyrophenones, metoclopramide, risperdone, reserpine
3. Compression of the pituitary stalk
4. Hypothyroidism (↑ TRH → ↑ PRL due to lactotroph hyperplasia)
5. Pituitary tumors co-secreting PRL (mixed GH-PRL)
6. Physiologic: postpartum, pregnancy, nipple stimulation
7. Renal insufficiency

Prolactinoma

- Most frequent secretory pituitary tumor
- Microadenoma in women
  - Present earlier w/ amenorrhea/galactorrhea
- Macroadenoma in men
  - Present later w/ headaches → visual loss
  - Also have sexual dysfunction, gynecomastia, infertility
- Other consequences: osteoporosis
- DA agonists (cabergoline, bromocriptine)
  - Improve PRL / Sxs and potentially shrink the tumor
- Surgery is reserved for:
  - Resistance / intolerance to DA agonists
  - Women w/ macroadenoma who desire pregnancy
  - Cystic prolactinomas or acute visual loss

Q2 - Answer
A 55 y.o. man undergoes pre-op eval for carpal tunnel release and is found w/ BP 160/90 and fasting BG 120 mg/dl. He admits to chronic frontal headaches, excessive sweating, and joint pain. On exam: coarse facial features, multiple skin tags, wide feet and hands.

- Which is the next best course of action:
  - 1. Measure random growth hormone (GH) level
  - 2. Measure growth hormone following 75-g glucose administration
  - 3. Measure insulin-like growth factor 1 (IGF-1 or somatomedin C)
  - 4. Order MRI of pituitary gland

Acromegaly

- Usually caused by GH-secreting pituitary macroadenoma

- A single GH level is inadequate due to pulsatile secretion
- Screening test: plasma IGF-1
  - Longer plasma half-life c/w GH
  - Falsely-low: uncontrolled DM, malnutrition
- Confirmation test: GH during OGGT (nl: <0.4 ng/ml)
Q3. All of the following are possible consequences of acromegaly EXCEPT:

1. Goiter
2. Sleep apnea
3. Galactorrhea
4. Cholelithiasis
5. Colon polyps
6. Left ventricular hypertrophy

Syndromal associations of acromegaly

- MEN 1 – autosomal dominant (11q13 – menin tumor suppression)
  - Pituitary tumors (PRL, GH, or ACTH–secreting)
  - Parathyroid hyperplasia (hypercalcemia)
  - Pancreatic islet-cell tumors (gastrinoma, insulinoma)

- Carney complex – autosomal dominant (PRKAR1 mutation)
  - Cardiac myxomas
  - Pigmented skin lesions
  - Pigmented nodular adrenal hyperplasia

- McCune-Albright syndrome – X-linked
  - Polyostotic fibrous dysplasia
  - Café-au-lait spots
  - Sexual precocity

Treatment of acromegaly

- Transsphenoidal surgery
- Med tx:
  - Somatostatin analogs (octreotide, lanreotide, pasireotide) – for incomplete biochemical response postoperatively
  - GH-Receptor antagonist – pegvisomant
  - Dopamine agonists – less effective
- Radiotherapy (XRT) – for incomplete response to surgery & med tx

Q4

A 65 y.o. man w/ hx of pituitary adenoma develops severe headache, nausea, vomiting and subsequently becomes confused. On exam: BP 170/89, RT 3rd CN palsy and meningismus. CT shows hemorrhage within large pituitary adenoma.

What is the best next course of action:
1. Emergent transsphenoidal surgery
2. Dopamine agonist
3. BP control
4. Dexamethasone 2 mg IV
Q4 - Answer
A 65 y.o. man w/ hx of pituitary adenoma develops severe headache, nausea, vomiting and subsequently becomes confused. On exam: BP 120/80, RT 3rd CN palsy and meningismus. CT shows a large partially cystic pituitary mass.

What is the best next course of action:
1. Emergent transsphenoidal surgery
2. Dopamine agonist
3. Cortisol, free T4 and prolactin measurement
4. Dexamethasone 2 mg IV

Pituitary apoplexy
- Rare, but potentially life-threatening
- Clinical manifestations
  - Severe headache
  - Vision loss
  - Sxs of adrenal insufficiency
- Diagnostic studies: pituitary CT or MRI
- Tx
  - Stress-dose glucocorticoids, IV fluids
  - Neurosurgical consult

Hypopituitarism

<table>
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<tr>
<th>Pituitary causes</th>
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<td>Trauma</td>
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Lymphocytic hypophysitis
- Postpartum
- Autoimmune
- Presentation
  - Headaches
  - Pituitary defect (ACTH, TSH)
  - Pos DI, ↑ prolactin
- MRI: pituitary or stalk enlargement
- Tx
  - Hormonal replacement
  - High-dose glucocorticoids for severe headaches

Sheehan’s syndrome
- Postpartum
- Ischemia 2° obstetrical hemorrhage
- Presentation
  - Acute: ↓BP, nausea, lethargy, inability to lactate
  - Subacute: failure to lactate/resume menses
- MRI: small pituitary or empty sella
- Hormonal replacement

Management of hypopituitarism

- Labs to test end-organ function
  - Adrenal: Cortrosyn stim or insulin tolerance test
  - Thyroid: TSH + free T4
  - Gonadotropin: LH, FSH, testosterone or estradiol
  - GH: IGF-1, GH stimulation tests

- Imaging: pituitary MRI
- Tx
  - Glucocorticoid BEFORE thyroid hormone replacement
  - Use end-organ hormones (exceptions: GH and to induce fertility)
  - Monitor tx clinically + biochemically (end-organ hormones: free T4, testosterone, IGF-1 levels)

Diabetes Insipidus

- Presentation:
  - Polydipsia / polyuria AND dilute urine
  - After pituitary surgery or context of craniopharyngioma, head injury, pregnancy (placental vasopressinase)

- Dx:
  - 24-hr urine volume during ad libitum fluid intake
  - Water deprivation test to R/O psychogenic polydipsia & establish central vs. nephrogenic DI

- Tx of central DI
  - DDAVP nasal spray or tablets
  - Allow intermittent polyuria to avoid hyponatremia
A 36 y.o. F complains of wt gain, hirsutism, oligomenorrhea & easy bruising. On exam: BMI 33, BP 144/90 mm Hg, facial hirsutism, acne, striae, supraclavicular fat deposits, and nl muscle strength.

Labs: random glucose 187 mg/dl, K 3.9 mEq/l, a.m. cortisol 6.2 mcg/dl (nl: 5-18) and ACTH 25 pg/ml (nl: 15-65).

What is the correct next step:
1. MRI of pituitary
2. CT of adrenals
3. 24-hr urine free cortisol
4. No further work-up

Establishing dx of Cushing’s syndrome

Screening tests should have high sensitivity

AND

Differentiate between CS and reactive hypercortisolemia
- Severe obesity
- Psychiatric disorders: depression, anxiety disorder, anorexia nervosa, OCD
- Chronic alcoholism
- Poorly controlled DM
- Obstructive sleep apnea

Who and how to screen for CS

Clinical presentation
- Wt gain w central fat distribution, easy bruising, wide purple striae, opportunistic infections, muscle wasting, irregular periods, new acne or hirsutism
- Uncontrolled type 2 DM, fractures
- Adrenal incidentalomas

Screening tests
- 24-hr urine free cortisol
- 1-mg dexamethasone suppression test
- Bedtime salivary cortisol

Establishing the cause of CS

1. ACTH-dependent or independent

2. If ACTH-dependent, what is the source of ACTH?
   - Pituitary adenoma (Cushing’s disease)
   - Ectopic (bronchial carcinoid, lung cancer, GI/pancreatic carcinoid)
**Basal morning ACTH concentrations (IRMA)**

- Cushing’s disease
- Ectopic ACTH syndrome
- Adrenal adenoma
- Adrenal carcinoma

ACTH < 5 pg/ml - adrenal Cushing
ACTH > 15 pg/ml - pituitary or ectopic

**To convert to pg/ml, multiply by 4.5**

**Cushing disease (CD) vs. ectopic ACTH syndrome**

- High-dose DXM suppression test
  - Ectopic ACTH: cortisol & ACTH will NOT suppress
- CRH stimulation test
  - Ectopic ACTH: cortisol & ACTH will NOT ↑
- Inferior petrosal sinus sampling (IPSS)
  - Central → peripheral ACTH gradient

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**Q6**

- A 50 y.o. M is referred for eval of refract HTN. Meds: 50 mg spironolactone, 40 mg lisinopril and 30 mg nifedipine. He couldn't tolerate HCTZ due to ↓ K+. BP 150/90. Renal US (-) for renal vascular DZ, but shows a 2 cm RT adrenal mass.

What is the next evaluation test:
1. PAC (plasma aldosterone)/PRA (plasma renin activity) ratio after stopping all BP meds
2. PAC/PRA ratio after stopping spironolactone
3. Urine aldosterone after stopping spironolactone
4. Bilateral adrenal vein sampling w/ aldosterone determination

**Q6 Answer**

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**Q7**

- A 26 y.o. M had several mo. of episodic headaches and palpitations. Also, anxiety and diaphoresis during the episodes. His BP fluctuated a lot during knee surgery after a soccer accident few wks. ago. On exam, BP 129/82 and pulse 80. He has no goiter. His TSH is nl.

What is the next best course of action:
1. Measure BP for 3 consecutive days
2. Measure plasma catecholamines
3. Measure 24-hr metanephrines
4. Perform glucagon stimulation test

**Q7 - Answer**

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Pheochromocytoma - presentation

- 0.1% of pts w/ HTN
- Classic triad:
  - Headaches, palpitations, diaphoresis
- Other suggestive scenarios:
  - Postural hypotension
  - BP fluctuations during general anesthesia
  - HTN in young pts
  - HTN resistant to usual tx
  - FHx of pheo.

Pheochromocytoma: dx and tx

- Hormonal tests
  - 24-hr urine metanephrines and catecholamines
  - Plasma metanephrines
  - Clonidine suppression test
    - ↑ clinical suspicion w/ indeterminate metanephrine results
  - Chromogranin A: poor specificity
  - Imaging:
    - CT: large, lipid-poor tumor
    - MRI: hyperintense on T2-weighted images
    - 131I-MIBg scan: ↑ specificity, used
  - Tx
    - Pre-op preparation: volume expansion, α-blockade, followed by α/β-blockade, CCB
    - Adrenalectomy

Syndromal associations of pheo

- MEN 2A (10q11.2 – activation mutation of RET)
  - Autosomal dominant (AD)
  - Medullary thyroid CA, bl pheo, parathyroid hyperplasia
- MEN 2B – sporadic or AD
  - Medullary thyroid cancer, bl pheo, mucosal neuromas
- Neurofibromatosis type 1 (von Recklinghausen's disease)
  - AD
  - Neurofibromas, café au lait spots, axillary freckling, iris hamartomas (Lish nodules)
  - von Hippel-Lindau syndrome:
    - AD, VHL tumor suppressor gene (3p25-26)
    - Hemangioblastomas, bl pheo, renal cell CA
- Carney's triad: paragangliomas, adrenal adenomas, malignant gastric stromal tumors, benign pulmonary chondromas

Q8

- A 50 y.o. F found incidentally w 2.5 cm adrenal mass during work-up for acute abd pain. The mass is hypo-intense on CT (0 HU). She takes no meds. On exam, she looks overweight, BP 120/80, no hirsutism/ abd striae/ muscle weakness. Labs: nl CBC & chemistry.

  Which of the following should be ordered next:
  1. PAC / PRA ratio
  2. Serum cortisol after 1-mg DXM test
  3. Plasma or urine metanephrines
  4. All of the above
  5. (1+2)
  6. (2+3)

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Adrenal Incidentaloma

- Secreting excessive hormones?
  - Overnight 1-mg DXM suppression test
  - Urine or plasma fractionated metanephrines
    - PAC/PRA ratio if pt has HTN or ↓K+
- Malignant?
  - Size matters
    - Attenuation value: lipid-rich (<10 HU) benign; lipid-poor (>20 HU) pos malignant
    - Opposed phase MRI: for indeterminate attenuation (10-20 HU)
Surgical indications for adrenal incidentalomas

- Biochemically proven pheo
- Size or attenuation value worrisome for malignancy
- Biochemically proven Cushing’s syndrome

Adrenal biopsy (CT-guided)
- Rarely needed
- Known primary Ca and concern for metastasis
- R/O pheo first w urine/plasma tests

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Adrenal imaging

1. Non-contrast CT
   Hypodense LT adrenal adenoma

2. Contrast CT
   Complex RT adrenal CA w liver invasion

3. MRI
   Right adrenal pheo w/ ↑ signal on T2-weighted image

Q9

A 67 y.o. F w/ severe COPD + Hashimoto’s thyroiditis presents w/ 2-mo hx of fatigue, anorexia, nausea, 5-lb wt loss and muscle weakness. Meds: levothyroxine 100 mcg/day. On exam: BP 98/60, pulse 90 and slight pallor. Labs: Na 130 mEq/l, K 4.5 mEq/l, HCO₃ 24 mEq/L and alb 3.1 g/dl. Cortrosyn stim: baseline cortisol 3.5 mcg/dl; 1 hr: 13.0 mcg/dl.

Which of the following statements are true:
1. She has Addison’s disease
2. She does not have adrenal insufficiency because her delta cortisol is > 9 mcg/dl
3. She will require tx with prednisone 7.5 mg/d and fludrocortisone 0.1 mg daily
4. She requires glucocorticoid replacement and further w/u is needed

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Etiology of adrenal insufficiency

Primary (Addison’s)
- Autoimmune (>70%)
  - Isolated
  - Polyglandular autoimmune I: parathyroid, adrenal, gonads, skin
  - Polyglandular autoimmune II: adrenal, gonads, thyroid, pancreas
  - Infectious (TB, fungal, HIV)
- Hemorrhagic or thrombotic
  - Septicemia (meningococcus, pseudomonas)
  - Anticoagulant tx
  - Antiphospholipid syndrome
  - Metastatic: lung, breast, colon, kidney
- Meds: ketoconazole, etomidate, mitotane, megestrol

Secondary/Tertiary
- Glucocorticoid withdrawal
  - Most common cause of adrenal insufficiency
  - ≥ 16 mcg pred/d ≥ 3 wks or any dose qHS ≥ 3 wks
  - Intracranial injections
- Hypotension due to radiation, surgery or pituitary mass/ infiltration
  - Isolated ACTH deficiency (autoimmune)
- Other: megestrol

Important differences

Primary (Addison’s)
- ↓ aldosterone
  - ↑ K⁺
- Hypotension (orthostatic)
  - ↑ ACTH secretion
  - Skin hyperpigmentation

Secondary/Tertiary
- NI aldosterone
  - NI K, but Na can be ↓
  - Less hypotension
- ↓ ACTH secretion
  - No hyperpigmentation
  - Hypoglycemia
**Work-up for Adrenal Insufficiency (AI)**

1. Demonstrate inappropriately low cortisol secretion
   - AM plasma cortisol < 3 mcg/dl
   - ACTH (Cosyntropin) stim: cortisol < 18 mcg/dl
   - Gold standard: insulin tolerance test

2. Differentiate between primary and secondary
   - AM plasma ACTH ↑↑ in primary AI (check PAC/PRA)
   - AM plasma ACTH i or nl in secondary AI (check pituitary hormones)

3. Seek the cause
   - Adrenal imaging (CT, MRI) for primary AI
   - Pituitary imaging (MRI) for secondary AI

**Treatment of adrenal insufficiency**

**Primary**
- Hydrocortisone 10-20 mg/m²/d divided in 2-3 doses -OR-
- Pred 2.5-7.5 mg/d -OR-
- DXM 0.25-0.75 mg/d
- Use lowest dose that alleviates sxns
- Fludrocortisone 0.05-0.2 mg/d
- Aim for normal K and PRA

**Secondary**
- Hydrocortisone 10 mg/m²/d
- No need for fludrocortisone

**Adrenal Replacement during acute illness for the patient w/ adrenal insufficiency (AI)**

- **Minor acute illness**
  - The “3 x 3” rule

- **Major acute illness or adrenal crisis**
  - Initial dose: 4 mg DXM or 100 mg hydrocortisone
  - Cont. w/ 50 mg hydrocortisone IV q6-8 hrs
    (also has adequate mineralocorticoid effect)

**Last-minute Advice**

- Pituitary hormones can be “inappropriately normal”
  - Look for “end-organ hormones”

- Pituitary hormones have diurnal variations
  - Suppression tests to dx acromegaly & Cushing’s syndrome
  - Stimulation tests to dx GH & cortisol deficiency

- Always order hormonal tests before endo imaging
- Tumor size does matter
- All women with amenorrhea are pregnant until proven otherwise