Academic Half Day: Adrenal & Pituitary Disorders
Facilitator Guide

Type	Cortisol Level	Aldosterone level	Renin	ACTH	DHEA, DHEAS	Other	Morning Stim (1mcg)
Primary	Low	Low	High	High	Low	Hyperpigmmentation, Low Na, elevated K; more likely to be hypotensive or present in adrenal crisis	Minimal/no response
Central	Low	Normal	Normal	Low or Nl	Can be low	Can have low Na but normal K	Modest response

Case 1

A 65 yo man with a recent diagnosis of atrial fibrillation 2 months ago presents with 1-2 months of progressive generalized weakness and postural dizziness that are now affecting his ADL's. He has lost 10 lbs during this time. He has a history of HTN, CVA, and atrial fibrillation. He is a prior smoker. He has a family history of lung cancer. He is on Coumadin (recently started), diltiazem ER, lisinopril, and simvastatin.

PE: is significant for a BP of 84/60, irregular HR 105/min, and hyperpigmentation of gums, lips, and skin creases.

Labs: Hb 10.6, Na 133, K 5.0, INR of 7.3, and sepsis work-up is negative

1) **What general diagnoses are you considering? Why?**

- Vitals suggest developing shock: ddx cardiogenic, obstructive, hypovolemic, distributive
    - Malignancy (family history of lung cancer, prior smoker) with hyponatremia; perhaps shock is obstructive from pericardial tamponade, pulm embolism
    - Hypovolemic from internal bleed related to coumadin (Retroperitoneal,gastrointestinal?)
    - Mix hypovolemic + Distributive from Adrenal Insufficiency
        - Volume loss from hypoaldosteronism
            - Coumadin – adrenal hemorrhage
- In general consider Adrenal Insufficiency (see below for the underlying differential).
- Symptoms of AI are non-specific: weakness, fatigue, anorexia, nausea, vomiting, weight loss and abdominal pain, orthostatic hypotension
- Physical exam findings which can be suggestive: hyperpgimentation (ACTH hypersecretion; *mechanism reviewed in Q3*), hypotension and tachycardia if adrenal crisis – an endocrine emergency

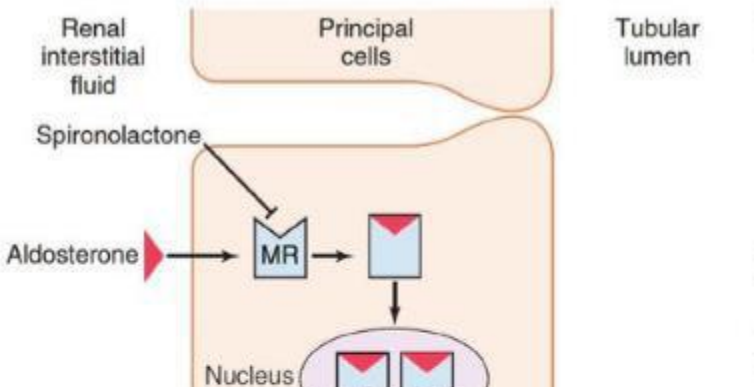
2) **How do we categorize this general diagnosis?**

- Adrenal Insufficiency: Partial or complete lack of production/secretion of adrenocortical steroids. Can be Primary, Central, or Iatrogenic:

- Primary Insufficiency – failure/disease of adrenal gland itself
    - There are three layers of the adrenal cortex which secrete three distinct classes of corticosteroids under separate regulatory mechanisms
        - Zona Glomerulosa – Mineralocorticoids - Aldosterone
            - Under RAAS regulation (I.e. not impacted by pit malfunction or central AI)
        - Zona Fasciculata – Glucocorticoids - Cortisol
            - H-P axis Regulation
            - Offers negative feedback on Hypothalamus (CRH) & Pituitary (Cortisol)
        - Zona Reticularis – Sex hormones - DHEA/DHEAS
            - H-P axis Regulation
    - Thus in primary insufficiency, when the adrenal gland itself is affected (and thus all three cortex layers), you see symptoms of glucocorticoid deficiency (nonspecific) and mineralocorticoid deficiency (hyperkalemia, hyponatremia, hypotension, salt craving).
        - *We review mechanism of aldosterone and therefore lack of aldosterone leading to hypoNa, hyperK in next question.*
    - In US, majority caused by autoimmune destruction = Addison's Disease;
        - Worldwide cause = TB
- Central Adrenal Insufficiency
    - Secondary (pit)– Diminished ACTH by process destroying pituitary corticotrophs
    - Tertiary (hypothal)– diminished CRH due to hypothalamic disease
    - Decreased stimulation of the fasciculata (via decreased CRH/ACTH) to make cortisol
    - The glomerulosa (aldosterone) is not affected because it is under control of RAAS -> therefore central AI is less likely to cause hyperkalemia, salt craving, and shock
- Iatrogenic - #1 cause in adults – exogenous glucocorticoids (a form of central)
    - Exogenous steroid suppresses CRH and ACTH (it's a negative feedback loop) -> atrophy of zona fasciculata and reticularis -> Impaired ability to secrete cortisol (especially under
      stress)
    - Aldosterone is again NOT largely affected

3) Explain the mechanism of hyperpigmentation, hyponatremia, and hyperkalemia. The presence of these signs therefore suggest what?

- They suggest he has "Primary Adrenal Insufficiency"
- **Hyperpigmentation**: in primary insufficiency no cortisol is made = no negative feedback on HP-axis (CRH/ACTH) -> increase in POMC (proopiomelanocortin) --> ACTH and alphaMSH -> increased melanin production from melanocytes
    - This doesn't happen in Central AI – ACTH (and precursors) are low in central AI
- **Hyponatremia** (~80% of chronic primary AI) & **Hyperkalemia** (~60%) – they don't have aldosterone -> kidney isn't retaining sodium and secreting potassium as well



Aldosterone increases sodium reabsorption and potassium excretion. It binds MC receptor and stimulates production of ENaC (transports Na from the urine to the blood) and Na/K exchange transported (will exchange Na from urine -> blood and K from blood -> urine).

- In Central AI -> can have mild hyponatremia (due to cortisol deficiency)
  - Note: Hypothalamus releases CRH which will have some stimulus of ADH (in addition of ACTH) --> this is mechanism behind euvolemic hyponatremia and why we must rule out AI during SIADH work up.

- Other possible findings: anemia, eosinophilia (endogenous/exogenous steroids cause decreased release and chemotaxis of eosinophils so without that inhibition you instead get eosinophilia), hypoglycemia with fasting (uncommon)

4) **What is the differential for the underlying cause of AI based on these categories?**

Primary AI	Central AI
Autoimmune adrenalitis – Addison's Disease	Exogenous Glucocorticoid Therapy
Infection: TB, fungal, bacterial, HIV , Neisseria	Hypothalamic/pituitary diseases – granulomatous (sarcoid), infectious, infiltrative (amyloid, hemochromatosis), malignancy (lymphoma, pituitary carcinoma versus other brain metastatic)
Metastatic Cancer to adrenals: lung, breast, melanoma, GI (destroy most of gland to be symptomatic)	Cranial Irradiation or surgery which damages the pituitary stalk
Adrenal Hemorrhage/infarction – Meningococcemia (Waterhouse–Friderichsen syndrome), P.a., S.a., anticoagulant therapy puts at high risk, APL syndrome, post-op, HIT, DIC	Pituitary apoplexy (infarct), Sheehan's Syndrome (when significant peri/post-partum bleeding leads to hypotension and pituitary ischemia)
Meds: ketoconazole, etomidate, fluconazole -> inhibit steps in cortisol synthesis	Chronic drugs: long-term Megestrol in cachectic patients (has glucocorticoid activity and thus suppresses H-P axis), opiates (unclear mechanism)

5) **Describe your work-up to make the diagnosis.**

- Baseline Morning Serum Cortisol – cut-off values vary depending on resource
    - Level <3microg/dL highly suggestive (if exogenous steroids ruled out)
    - Level > 15 makes AI unlikely
        - Would be time to revisit other diagnoses (sepsis, hemorrhage)
    - Level 3-15 requires ACTH stimulation test with cosyntropin
    - Cortisol level varies based on pulsatile nature of ACTH secretion, diurnal variation of cortisol levels (highest in the morning and lowest in evening), stress at the time measurement
    - Assay determines total (protein-bound and free) cortisol level
    - > 90% cortisol is protein bound (to corticosteroid-binding globulin and albumin
        - pregnancy or with estrogen therapy – increase proteins and thus level (but not free level)
        - hypoproteinemia --> lower total serum baseline cortisol levels (critically ill, liver disease)
- Cosyntropin Stimulation Test
    - **Cosyntropin** is a synthetic portion of the natural hormone corticotropin (ACTH) - if the adrenal gland is the problem (primary adrenal insufficiency) then stimulation will not result in an increase in cortisol.

- After given "ACTH", a functioning adrenal gland should be able to raise cortisol level to > 18-20mcg/dL after 30-60mins
  - Perform any time of day with similar maximum cortisol levels
  - Failure to reach >18 suggests primary adrenal failure (primary tissue can never make the product even with stimulus)
  - Ability to reach >18 suggest central adrenal failure (primary tissue can make product once it has the stimulus)
- 250ug – may not detect partial adrenal insufficiency in patients with hypothalamic or pituitary disorders (especially 1st 2-4 weeks – hasn't atrophied)
- 1ug (low-dose) ACTH stimulation test
  - Improves sensitivity in detecting partial secondary/tertiary AI
  - Disputed by some – studies suggest that 30minute cortisol level is similar with low-dose and standard dose

- ACTH
  - elevated in Primary disease (pit is working, adrenal is not)
- Imaging:
  - Primary AI suspected –> consider CT abdomen
    - Addison Disease – small adrenals
    - Infiltrative (metastatic/granulomatous/hemorrhage) – enlarged
    - TB – calcifications
  - central AI suspected –> MRI brain (pituitary protocol)

6) **Putting it all together – Discuss what the results for the below labs/tests/clinical presentations would show in Primary vs Central AI.**

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In our patient, his serum ACTH level was elevated at 245, baseline serum cortisol was 0.4ug/dL and cosyntropin stim test resulted in a cortisol of 0 ug/dL suggesting primary adrenal insufficiency. A CT of his abdomen showed bilateral adrenal hemorrhages that were thought to be related to his recent initiation of anticoagulation and supratherapeutic INR. He did not have any evidence of DIC, HIT, malignancy, or embolic source to otherwise predispose to adrenal hemorrhage and resultant adrenal insufficiency.

Assuming the patient's adrenal glands will not recover, What's the most appropriate management at this time? This patient should be treated with mineralocorticoid and glucocorticoid replacement.

1) **What medications would you consider?**

- GC:
  - Hydrocortisone – identical to physiologic steroid, short half-life, can be tightly titrated, preference in chronic treatment
  - Prednisone & Dexamethasone – longer acting, convenient but difficult to titrate
- MC:
  - Fludrocortisone – in primary adrenal insufficiency

You stabilize this patient during the hospitalization onto physiologic dosing of hydrocortisone and fludricortisone. He returns months later with cold-like symptoms and is otherwise well.

2) **What is your advice regarding his medications now? What about if he were septic?**

- During a mild stress (a cold) the hydrocortisone (or other steroid) dose should be increased by 2-3x's the patient's base dose. There are different escalations in dosing based on the significance of the stress/surgery. Increasing fludricortisone is not necessary in stress dosing.
- Note during major surgery/sepsis – use hydrocortisone for ease of titration
  - Surgeries require stress dose prior/after and taper
    - Generally, we use: HC 50 mg q6 x 1 day, then 50 q 12 x 1 day, then taper to base dose over 3-5 days
  - If presents in Sepsis/shock – treat empirically (bolus dose of 100mg hydrocortisone), do not wait for cortisol level, give fluids with steroid
    - If previously undiagnosed AI and in crisis, use IV dexamethasone
    - Dexamethasone does not affect cortisol measurements (hydrocortisone does)
- There is little utility in measuring ACTH/cortisol levels for steroid titration in chronic AI

*** *Bonus comment: in unconfirmed adrenal insufficiency presenting with concern for concomitant hypothyroidism, must treat AI prior to initiating replacement thyroid hormones. Supplying thyroxine prior to repleting glucocorticoid def can precipitate crisis.*

Case 2

A 60-year-old man is evaluated for an eight week history of progressive muscle weakness. The patient has gained at least 40lbs and has developed hypertension and type 2 diabetes mellitus in the last 2 years. He first noticed lower extremity weakness and swelling 6 months ago. His diabetes is only partially controlled despite maximal metformin dosing and dietary changes; his blood glucose measurements at home are usually greater than 250 mg/dL. He adheres to his diet and checks his glucoses religiously. Exercise is limited by weakness. He also takes hydrochlorothiazide, lisinopril, amlodipine, and metoprolol.

ROS: Frequent colds, community acquired pneumonia in the last year, and recent history of shingles

PE: Appears chronically ill. BP 154/92 mmHg and BMI is 40. Skin shows facial acne. Patient exhibits central obesity, mild proximal muscle weakness, and 2+ peripheral edema.

Labs: SCr 1.3 mg/dL, a glucose level of 244 mg/dL, and a potassium level of 2.9 meq/L.

1) **What is the likely diagnosis? What about the clinical history suggests this?**

- Cushing syndrome: signs and symptoms occurring due to supra-physiologic glucocorticoid exposure
- This patient has resistant HTN (3 or more meds where 1/3 is a diuertic and poorly controlled) that is rather rapid in onset/progression. He also has onset/progression of diabetes (perhaps secondary diabetes) despite his efforts. He has central obesity, hirsutism, weakness, edema, and hypokalemia suggesting Cushing syndrome. The hypokalemia is likely due to mineralocorticoid effect of increased cortisol (and excessive urinary potassium loss). The HTN and DMII is likely secondary to Cushing syndrome.

2) **Does every patient with Cushing Syndrome present this way?**

- Classically, we think of symptoms as being some combination of:
    - proximal muscle weakness (increased catabolic effect on skeletal muscles), multiple ecchymoses, prominent supraclavicular fat pads, "moon facies," "buffalo hump,"central obesity, acne, hirsuitism, immune suppression, violaceous striae, hypokalemia, unexplained osteoporosis, new-onset hypertension, diabetes mellitus, CAD, OSA, recurrent infections, increased VTEs, bitemporal hemianopsia, etc. Helpful mnemonic:
        - C - cataract
        - U - ulcers
        - S- striae, skinn thinning
        - H- HTN, hirsuit
        - I - immunosuppresion
        - N – necrosis of femoral heads
        - G – glucose elevation (new onset DM)
        - O – osteoporosis, central obesity
        - I - impaired wound healing
        - D – depression / mood
- However, it can be due to ectopic ACTH production in setting of malignancy. These patients may present with cachexia, weight loss, temporal wasting and hypokalemia and/or hypertension. These patients with elevated ectopic ACTH may also have signs of hyperpigmentation.

3) **List 3 tests used to diagnose Cushing Syndrome.**

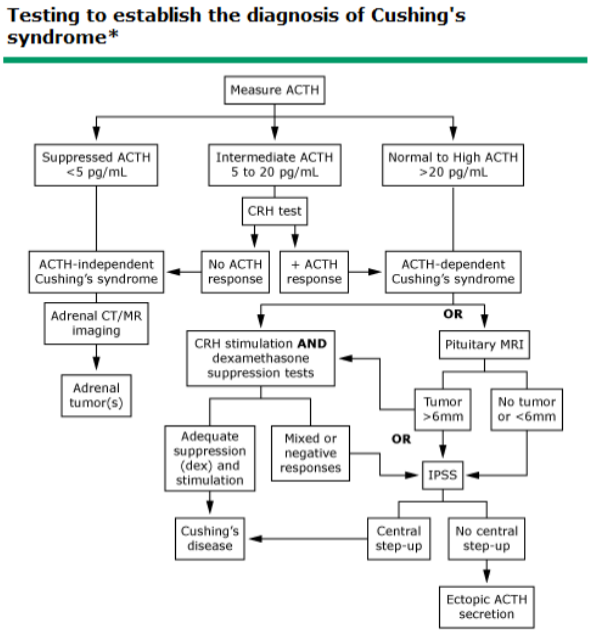
- Urine free cortisol excretion in a 24-hour period
    - Results may be falsely high in patients who are depressed or who abuse alcohol or people who drink large volume (5L/d)
    - Gold standard – 3-4 fold increase lab normal is diagnostic
- Dexamethasone suppression test: demonstrates loss of feedback inhibition of cortisol on the hypothalamic-pituitary axis
    - obtain a 8 or 9 AM serum cortisol level after 1 mg of dexamethasone has been administered at 11 PM the night before
    - Should not be used as sole criterion for Cushing diagnosis
        - Normal response = < 1.8 ug/dL (should suppress via negative feedback inhibition on CRH – ACTH release)
        - Abnormal (Cushing/hypercortisolism) if >1.8

-Caution use of this test if on estrogens/pregnancy which increase CBG (increase serum cortisol but not Urine cortisol); or if on Phenytoin/phenobarb/carbamazepine – induce P450 and increase the metab of dexamethasone.

- Late-night salivary cortisol measurement: loss of normal diurnal variation in cortisol secretion o salivary cortisol elevated at night is abnormal
- In general, positive results in two these tests are needed to confirm the diagnosis.

4) **Once we make the diagnosis, how do we establish the cause of Cushing Syndrome? Is it from the pituitary, ectopic, or from the adrenal gland?**

- ACTH is the most important thing to be able to interpret
- ACTH > 20pg/mL = ACTH-dependent Cushing Syndrome (pituitary or ectopic)
- ACTH < 5pg/mL = ACTH-independent Cushing Syndrome (adrenal)
- ACTH 5-20 = intermediate -> may require further testing
- If suspect ACTH independent -->
    - CT of adrenal glands (or MRI – more expensive)
- If suspect ACTH -dependent –> Check Pituitary/sella turcica MRI
    - Negative pituitary MRI in up to 50% with Cushing disease (lesion/adenoma too small)
    - Macroadenoma (>1cm – some use different size criteria) – likely etiology and no further testing
    - Microadenoma (<1cm - some use different size-criteria) – still need to differentiate ectopic vs pituitary
        - High dose dex suppression test (8mg) -> more than 50% decrease in cortisol suggests pituitary
            - Ectopic will have less -> ACTCH levels/cortisol higher on average -> difficult to suppress
        - Inferior Petrosal sinus sampling (IPSS):
            - gold standard for differentiating ectopic from pituitary
            - Invasive and few with experience
    - Below is one of many algorithms you can refer to for work-up. Important stuff is interpreting ACTH and knowing to order imaging



Case 3

A 40-year-old man is evaluated for an 18 month history of uncontrolled hypertension. He did not respond to atenolol and clonidine previously. There is no family history of hypertension. He has never smoked and has no other medical problems. He is not obese, exercises 4 days per week, and adheres to a Mediterranean diet. Current medications are maximum doses of hydrochlorothiazide, lisinopril, and amlodipine.

PE: 160/94 mm Hg, HR is 72/min, and remainder of exam is normal.

Significant Labs: SCr 1.1 (baseline 1.1 prior to ACEI), potassium is 3.1 meq/L, HCO3 30, and eGFR >60.

1) **What is the general problem here? How is it defined?** Resistant hypertension – blood pressure that remains above goal despite the administration of three antihypertensive drugs, one of which is a diuretic.
2) **What's in the differential for the underlying cause?**

- Renal Artery Stenosis – no bruit, no dramatic increase in creatinine after acei, no RF's for vascular disease otherwise
- Cushing Syndrome – see previous case
- Pheochromocytoma – no HA's, tachycardia/palpitations, panic attacks, diaphoresis, undulating

pattern, etc

- Chronic Kidney Disease – none per case

  -Primary/Secondary Hyperaldosteronism –patient has hypokalemia and hypertension…

  absorbing too much sodium and secreting too much potassium in urine from elevated aldosterone, reason for high suspicion of primary hyperaldosteronism

3) **What's the next best test?**

- Morning aldosterone (high) & renin activity (low)
  - Aldosterone > 15ng/dL suggestive
- Aldo: Renin Ratio (proposed cut-offs vary)
  - >20 is suggestive, >30 has 90% sensitivity & specificity
  - Difficult to measure on antihypertensives
    - Not eplerenone or spironolactone (MC Receptor antagonist – block binding of aldo to MC receptor)
    - FP: beta blocker, NSAID
    - FN: diuretic, dihydropyridine calcium channel blockers, ACE/ARBs
- Confirming Tests
  - Sodium Suppression Tests (can do PO via diet/tablets or IV saline). High sodium should suppress aldosterone.
    - Plasma Aldo <5ng/dL in healthy adult – normal = can be suppressed
    - >10 ng/dL diagnostic – in other words, cannot be suppressed
  - Other confirmatory tests: fludrocortisone suppression, captropril challenge, 24-hour urine aldosterone excretion

General DDx: primary hyperaldosteronism, secondary hyperaldosteronism (renovascular, Liddle), or nonaldosterone MC excess.

If Decreased renin and aldosterone: Nonaldosterone mineralocorticoid excess — The combination of suppressed renin & aldosterone in a patient with hypertension and hypokalemia indicates the presence of some nonaldosterone mineralocorticoid (deoxycortisone tumor, cortisol in Cushing Syndrome, CAH)

Our patient's Aldosterone is 25ng/dL and Renin is 0.5ng/mL. The ratio is "50."

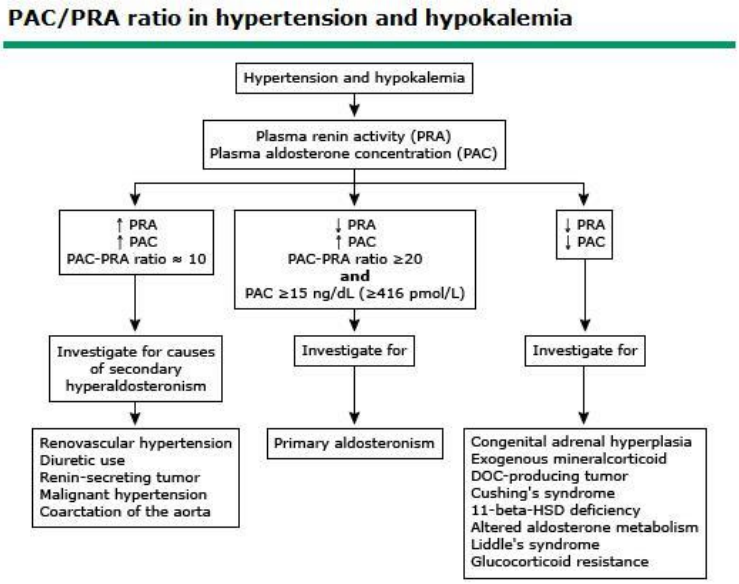
4) **What is the likely diagnosis?**

- Primary hyperaldosteronism - Autonomous aldosterone production by the adrenal zona glomerulosa independent of Renin-angiotensin system
  - Solitary aldosterone-producing adrenal adenoma (40%-50%) – more severe on average
  - Bilat adrenal hyperplasia / idiopathic primary hyperaldostero (50%-60%) – less severe
  - Unilateral hyperplasia or adrenal carcinoma (Rare)

5) **Who should be screened for primary hyperaldosteronism?**

- Everyone? 10% of all HTN
- Hypertension resistant to treatment
- associated with spontaneous (unprovoked) hypokalemia <3.5 (or significant hypokalemia <3 in response to low-dose diuretic) adrenal incidentaloma
- FmHx of early HTN/CVA

- FmHx of primary hyperaldosteronism



6) **How should our patient be treated?**

- Depends on imaging – Solitary adenoma/unilateral disease - surgery… can also try spironolactone/eplerenone
- Bilateral disease / bilateral adrenal hyperplasia – spironolactone or eplerenone

<u>Case 4</u>

A 47 yo male presents for a new patient appointment with a request to have his testosterone level checked. He has noted a several month history of low libido, now with erectile dysfunction. He also complains of fatigue. He says that his was working out at a gym and noted a sign about getting his "T checked."

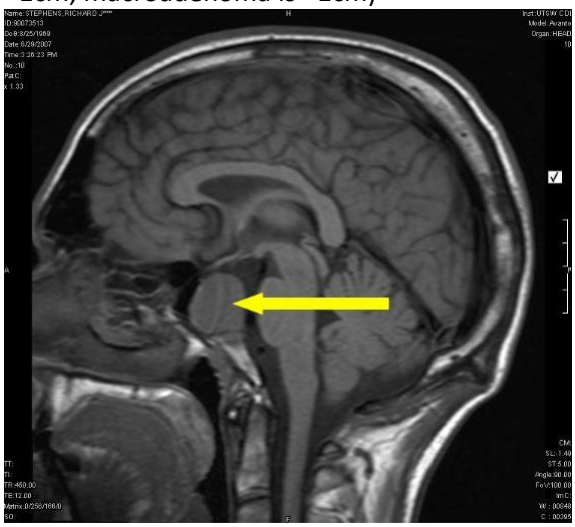
1. **Describe your approach to a complaint of erectile dysfunction.**
    a. Etiologies are typically in these general categories:
        i. Vascular (CV disease, HTN, DM, HLD, smoking, radiotherapy, surgery (radial prostatectomy)
        ii. Neurologic (spinal cord and brain injuries, PD, Alzheimer's disease, MS, CVA)
        iii. Hormonal (hypogonadism, hyperprolactinoma, hyper- and hypothyroidism, hyper- and hypocortisolism
        iv. Drug-induced (antihypertensives, antidepressants, antipsychotics, antiandrogens, recreational drugs, opiates, alcohol)
    b. Perform medical and sexual history
        i. make sure to ask about stressors, presence of nocturnal erections, etc
    c. Perform focused physical examination

He denies any medical history and does not take any medications. He is a non-smoker, doesn't drink alcohol other than a few times a year, and denies any recreational drug use. He is married and has two children. He is worried that continued ED may eventually result in problems in his marriage, but he says that his wife has been understanding and supportive.

On review of systems, he denies increased thirst or urination, denies palpitations, depression, constipation or hyperdefecation, anxiety, changes in his skin. He does think that he has decreased body hair. He endorses increase frequency of headaches. He denies changes in his vision.

On his exam, his vital signs are all within normal limits, his BMI 24. His neurologic, cardiovascular, including femoral and peripheral pulses, and pulmonary exam are all within normal limits. There is no gynecomastia. GU exam reveals a normal appearing penis, testes are descended with normal volume and no masses. Fundoscopic, visual field, and cranial nerve examinations are normal.

2. **What are your next steps in work-up, and why?**
    a. Lipid panel (since not recently assessed) for evaluation of cardiovascular risk = normal
    b. A1c or fasting glucose (since not recently assessed) = normal
    c. TSH = normal
    d. Testosterone level (total, and drawn in the morning)
        i. Total testosterone 132 mg/dL (drawn at 8:00am), repeat 125mg/dL (drawn at 8:00am) (low)
    e. Prolactin level (can be drawn at any time. Some recommend repeating but Endocrine Society recommends one time testing)
        i. Prolactin 204 ng/mL (high), and the same on repeat

3. **What is your diagnosis, and what is your next step?**
    a. Secondary hypogonadism due to hyperprolactinemia
    b. MRI of the brain shows a pituitary macroadenoma (microadenoma <1cm, macroadenoma is >1cm)
    c. 

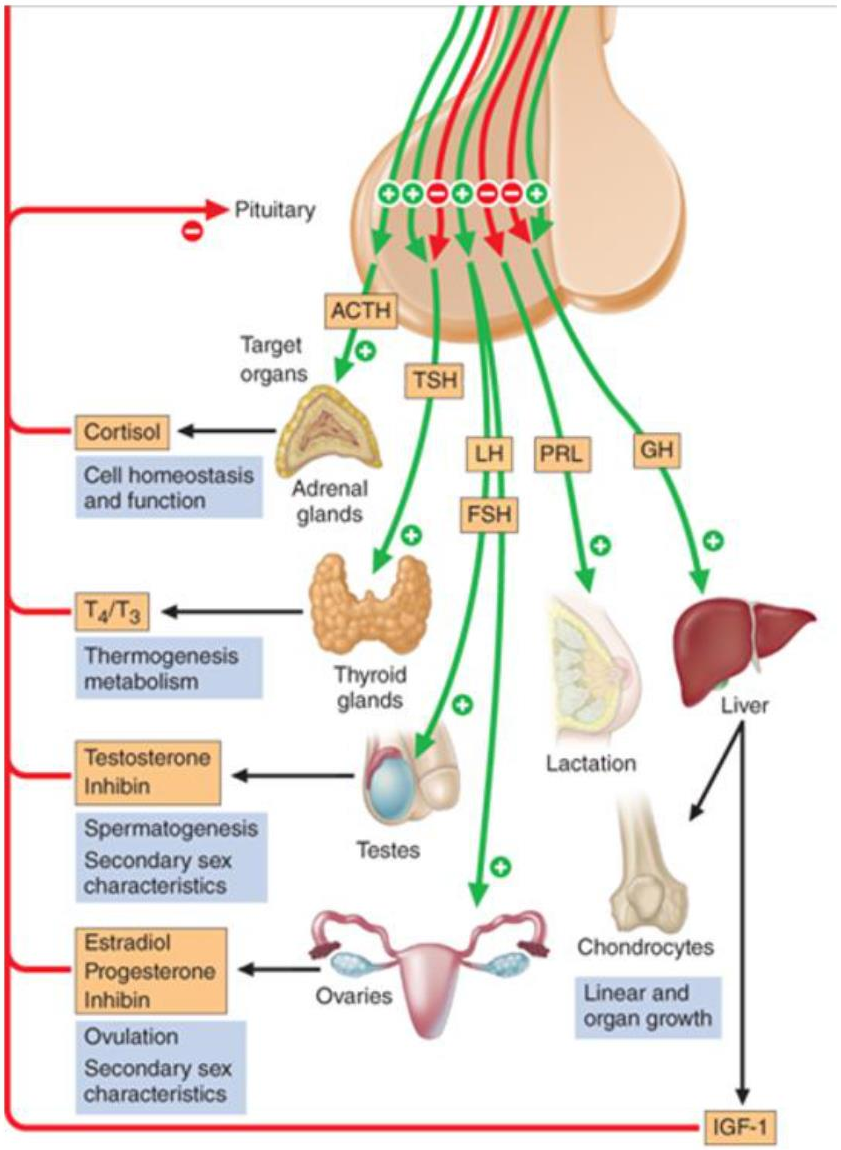
4. **What are some causes of hyperprolactinemia?**
    a. medications! Any dopamine antagonism will cause prolactin secretion
        i. TCA/SSRI/MAOinhibs, cimetidine (H2 blockers), dopamine antagonists (antipyschotics like risperidone, GI meds like metoclopramide, prochlorperazine,

chlorpromazine), verapamil, methyldopa (inhibs dopa to dopamine conversion), estrogens, opiates, cocaine, amphetamines

b. Pituitary adenomas
c. Cirrhosis (unconfirmed mechanism – estrogenism versus abnormal amino acid formation in CNS)
d. hypothalamic lesions
e. Hypothyroidism (long term under- or untreated can result in pituitary hyperplasia that may mimic a pituitary tumor, is reversed with replacement thyroid hormone)
f. chronic renal failure (decreased clearance and enhanced production of the hormone - not cleared by dialysis but will normalize after renal transplant)
g. Pregnancy, nipple stimulation (nonpathologic hyperprolactinemia)

5. **The patient asks about treatment. What do you recommend?**
    a. Macroadenomas should be treated with dopamine agonists first, no matter the size or presence of neurological symptoms
        i. dopamine agonist therapy is recommended prior to surgical intervention, can decrease tumor size by 50%
    b. Cabergoline is recommended as first line over Bromocriptine because it reaches better results
        i. measure prolactin level monthly and increase dose until normal
        ii. if vision was abnormal before therapy, should be reassessed within one month and MRI should be repeated in 12 months
        iii. therapy does not need to be lifelong - can consider decreasing to stopping if prolactin level has been normal for at least 1-2 years and the adenoma has decreased in size to no longer be visualized on MRI
    c. Can consider surgery if dopamine agonist treatment has been unsuccessful or for patients who can't tolerate high doses, or if a woman has a large adenoma (>3cm) and wishes to pursue pregnancy

Appendix:


Pituitary
ACTH
Target organs
TSH
LH
FSH
PRL
GH
Cortisol
Cell homeostasis and function
Adrenal glands
T_4/T_3
Thermogenesis metabolism
Thyroid glands
Testosterone
Inhibin
Spermatogenesis
Secondary sex characteristics
Testes
Lactation
Liver
Chondrocytes
Linear and organ growth
Estradiol
Progesterone
Inhibin
Ovulation
Secondary sex characteristics
Ovaries
IGF-1