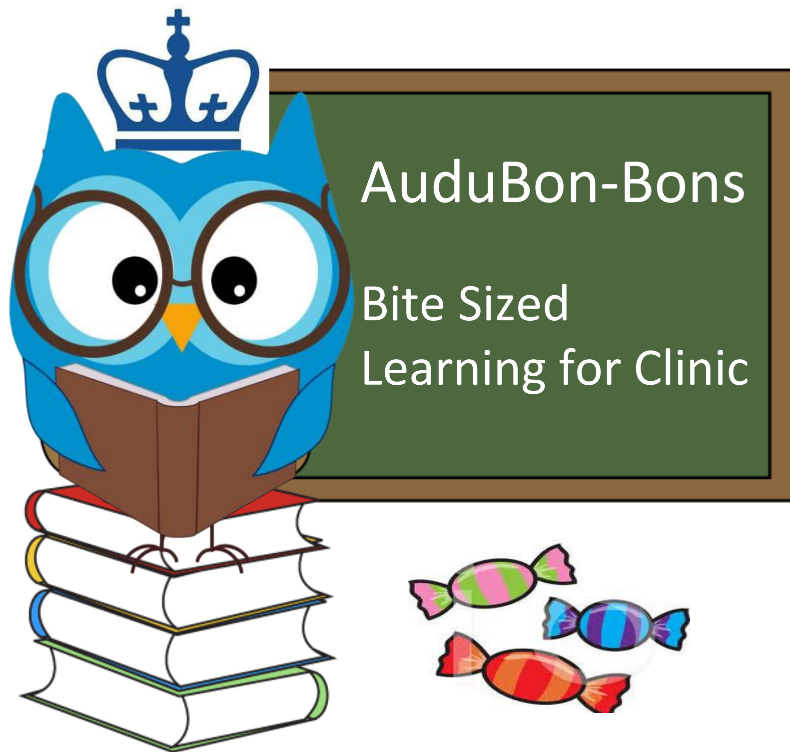
SECONDARY AMENORRHEA: HYPERPROLACTINEMIA

Week 88



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With SDH slide by Chloé Altchek, MS4

Reading Assignment:

Pearls of Exxcellence- Hyperprolactinemia.
https://www.exxcellence.org/list-of-pearls/hyperprolactinemia/

LEARNING OBJECTIVES

- Review the clinical manifestations of hyperprolactinemia in relation to reproductive health
- Understand the work-up for hyperprolactinemia
- Review common treatments for hyperprolactinemia

CASE VIGNETTE

- A 28 y.o. healthy G2P2 presents for follow-up visit after initial evaluation of spontaneous milk expression. This started over the last few months, and occurs a 1-2 times a week. She last breast fed 3 years ago after an uncomplicated NSVD of her second child. She also reports her periods have become irregular, occurring every 8-12 weeks over the last year, and she has some vaginal dryness.
  - You sent a prolactin level at intake visit which returned at 47
  - She returns today for next steps

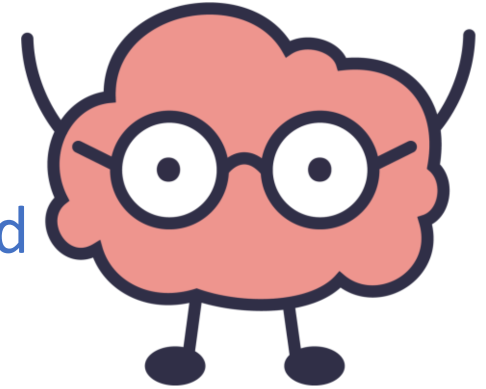
REVIEW FOCUSED HISTORY

- PMH: GERD
- PSH: Laparoscopic appendectomy 10 years ago
- OBH: NSVD x 2, uncomplicated, largest infant 7 lbs, most recent delivery in 2017
- GYNH: Menarche at age 12, previously "normal" monthly cycles lasting 5 days, now irregular every 8-12 weeks lasting 3-5 days.. Denies STDs, cysts or fibroids. Last pap 8/2019: NILM. Using condoms for contraception
- FH: Father with HTN, and DMII
- SH: Lives with partner and 2 children, feels safe at home, is a 8th grade math teacher, social etoh, no drugs or tob use
- Meds: TUMS PRN
- All: Sulfa- hives

PERTINENT PHYSICAL EXAM FINDINGS

- VS: Wt 59 kg, Ht 170 cm, BMI: 20.4, BP 105/74, P 82, T 37.0
  - Gen: NAD
  - HEENT: WNL, nl thyroid, nl visual field
  - Chest: CTAB
  - CVS: RRR
  - Breast: No visible masses, no palpable masses or LAD, some scant expression of milk bilaterally
  - Abd: Soft, non-tender, no masses
  - Ext Pelvic: Normal appearing external genitalia
  - Ext: WWP

PROLACTIN BASICS



- Prolactin is produced by lactotrophs in the pituitary gland
  - Metabolized by the kidney (25%) and the liver (75%)
- Normal PRL level is <20
- What happens to prolactin in pregnancy?
  - Pituitary gland can double in size during pregnancy
  - PRL increases over pregnancy, peaking at timing of delivery
    - Likely related to increased serum estradiol concentration
    - During pregnancy, serum PRL increase with a range between 35-600 ng/ml at term
  - Nipple stimulation (suckling) transiently increases PRL up to 300 ng/ml

CAUSES OF HYPERPROLACTINEMIA

- What can cause elevated prolactin?
  - Physiologic:
    - Pregnancy!
    - Nipple stimulation
    - Vigorous exercise or stress
    - Sex

Pathologic:

- Hypothalamic-pituitary stalk damage:
  - Trauma, radiation, Rathke's cyst, infiltrative diseases (TB, Sarcoid), parasellar tumors
- Pituitary disorders:
  - prolactinomas (micro/macro adenomas), acromegaly
- Systemic disorders:
  - Primary hypothyroidism, chest wall injury due to trauma/ surgery, herpes zoster, chronic renal/liver failure, malignancy
- Medication induced:
  - Antipsychotics, gastric motility agents, anti-hypertensives, dopamine receptor blockers, opiates, H2 antihistamines
- Idiopathic

MEDS AND PROLACTION

- Which common medications can cause elevations in prolactin?
  - Estrogen
  - Risperidone, haloperidol, fluphenazine
  - Antiemetic/ DA receptor blocking agents: metoclopramide, domperidone, prochlorperazine
  - TCAs/ SSRIs: amitriptyline, clomipramine, fluoxetine
  - Anticonvulsants: Phenytoin
  - Anti-HTN: Verapamil, methyldopa, labetalol
  - H2 Antihistamines: ranitidine
  - Opioids: methadone, morphine, heroin

CLINICAL MANIFESTATIONS OF HYPERPROLECTINEMIA

- What are the clinical manifestations of elevated prolactin?
  - Hypogonadism in premenopausal women
    - Oligomenorrhea
    - Primary and secondary amenorrhea
    - Anovulatory infertility
    - Galactorrhea
  - Generally asymptomatic in postmenopausal women

EVALUATION OF ELEVATED PRL

- Back to our patient, what are your next steps?
  - Urine pregnancy test
  - Review medication list
- Labs you will you order?
  - **Prolactin level***
  - HCG
  - TSH
  - Cr/ LFTs

*If initial prolactin is only mildly elevated (21 to 40), repeat fasting to confirm as meals can cause slight elevation in prolactin

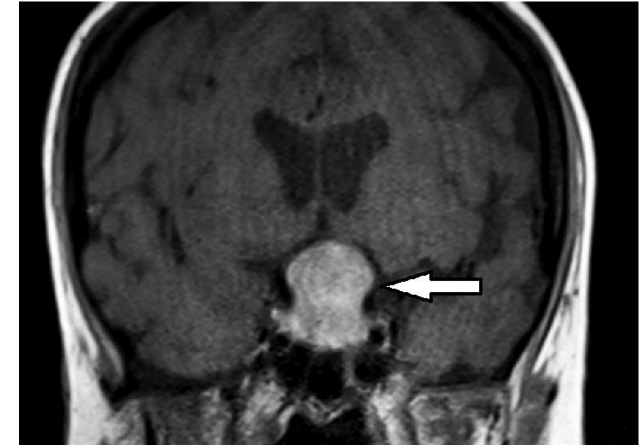
https://www.aafp.org/afp/2012/0601/p1073.html

HYPEPROLACTINEMIA WORK UP CONT…

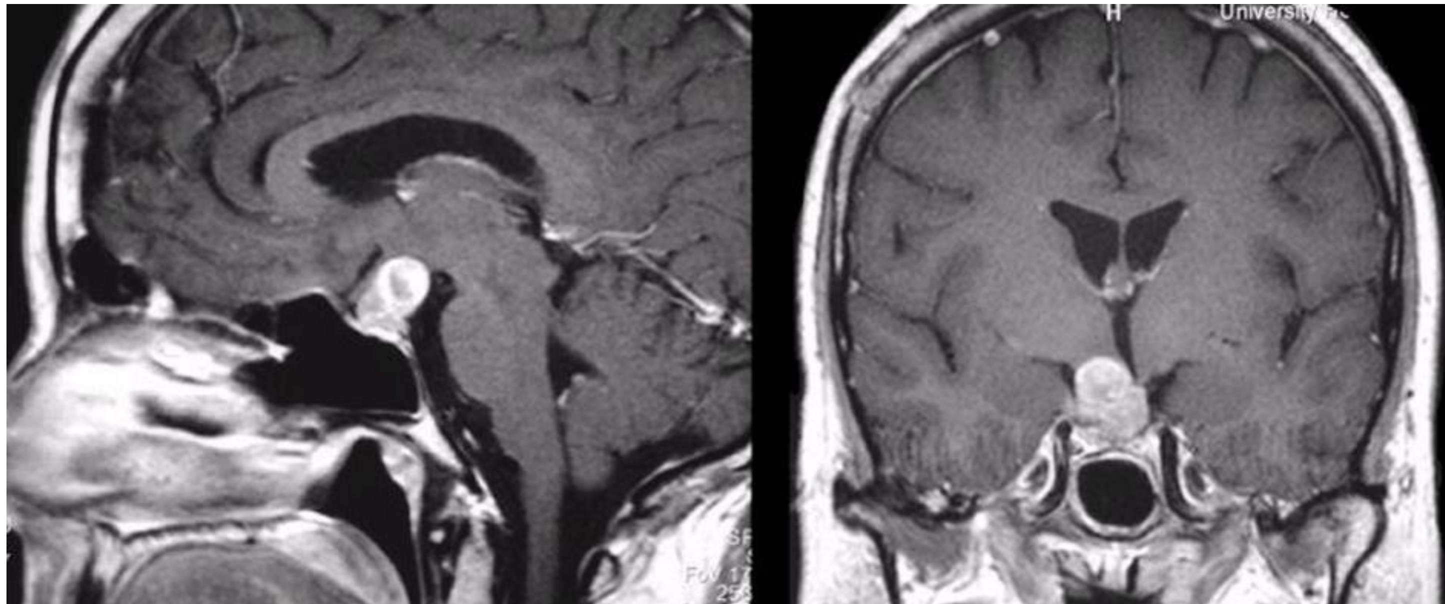
- What other symptoms should you screen for?
  - Headaches, vision changes, symptoms of hypothyroidism
- What should you look for on physical Exam?
  - Signs of hypothyroidism, hypogonadism, visual field loss, and chest wall injury
- What is the imaging modality of choice if no other cause found for elevated prolactin?
  - MRI of the sella turnica

PROLACTINOMAS

- What lesions are you looking for on MRI imaging?
  - Microadenomas (aka prolactinomas)= < 10 mm
  - Macroadenoms >/= 10 mm



https://www.researchgate.net/figure/Figure-of-8-Coronal-T1WI-of-MRI-shows-pituitary-macroadenoma-resembling-figure-of-8-or_fig11_320302987



http://casemed.case.edu/clerkships/neurology/Web%20Neurorad/PituitaryAdenoma.htm

PROLACTINOMA MANAGEMENT

- Medication
  - 90% of patients will have >50% reduction in tumor size at 1 year
  - 70-100% of patients experience significant reduction in prolactin levels
  - Dopamine agonists
    - **Bromocriptine** (less expensive), taken daily, preferred in pregnancy
    - **Cabergoline** (more effective in reducing PRL and adenoma size, fewer side effects), taken weekly
- What are the side effects associated with DA agonists?
  - Headache, pins and needles, hypotension, tachycardia
- What are the contraindications to medical management?
  - Pituitary stalk compression!
- Surgical management with transsphenoidal surgery
  - Drug failure
  - Women planning pregnancy with giant lactotroph adenoma (>3 cm)

SOCIAL DETERMINANTS OF HEALTH

HYPERPROLACTINEMIA IN WOMEN TREATED WITH ANTIPSYCHOTICS

- **Hyperprolactinemia is very common in women taking antipsychotics**: 38% had prolactin levels above the upper limit of normal, 2/3 of whom had significantly elevated levels with potential clinical consequences
- In patients with schizophrenia, **prolactin-related effects of antipsychotics decrease adherence by 30%**
- Symptomatic hyperprolactinemia has been found to **significantly increase the risk of suicide** in people with schizophrenia
- 2018 DAAMSEL RCT found that in women on antipsychotics with symptomatic hyperprolactinemia, **aripiprazole is effective in reducing serum prolactin levels and prolactin-related side effects** relative to the placebo group, leading to increased antipsychotic adherence and improved psychiatric outcomes

Risperidone and paliperidone are the biggest culprits due to their low blood-brain barrier penetration, resulting in higher concentration and subsequent effect on the pituitary

Many symptoms of hyperprolactinemia are difficult for people to discuss with healthcare providers (menstrual abnormalities, galactorrhea, and sexual dysfunction), thus they may go unaddressed for years. Be sure to screen patients who are taking antipsychotics for these symptoms.

Kelly DL, Powell MM, Wehring HJ, Sayer MA. Adjunct Aripiprazole Reduces Prolactin and Prolactin-Related Adverse Effects in Premenopausal Women With Psychosis: Results From the DAAMSEL Clinical Trial. J Clin Psychopharmacol. 2018 Aug;38(4):317-326.

Epic .Phrase

.BBonHyperprolactinemia

Description: Hyperprolactinemia evaluation

We discussed the potential causes of hyperprolactinemia including physiologic (pregnancy and breast manipulation) and pathologic causes as well as the initial work-up with HCG, TSH, Cr and possible pituitary imaging with MRI if other cause identified.

BILLING AND CODING

- E22.1- Hyperprolactinemia
- O92.6- Galactorrhea
- N91.5- Oligomenorrhea

EVIDENCE

- Huang W, Molitch ME. Evaluation and Management of Galactorrhea. *Am Fam Physician.* 2012 Jun 1;85(11):1073-1080.
- Hillard PJ, Lara-Torre E. Hyperprolactinemia. *SASGOG Pearls of Exxcellence.* 2012. Accessed on 7/23/2020: https://www.exxcellence.org/list-of-pearls/hyperprolactinemia/
- Thapa S, Bhusal K. Hyperprolactinemia. *StatPearls.* May 2020. Accessed on: https://www.ncbi.nlm.nih.gov/books/NBK537331/
- Kelly, D. L., Powell, M. M., Wehring, H. J., Sayer, M. A., Kearns, A. M., Hackman, A. L., Buchanan, R. W., Nichols, R. B., Adams, H. A., Richardson, C. M., Vyas, G., McMahon, R. P., Earl, A. K., Sullivan, K. M., Liu, F., Luttrell, S. E., Dickerson, F. B., Feldman, S. M., Narang, S., Koola, M. M., … McEvoy, J. P. (2018). Adjunct Aripiprazole Reduces Prolactin and Prolactin-Related Adverse Effects in Premenopausal Women With Psychosis: Results From the DAAMSEL Clinical Trial. *Journal of clinical psychopharmacology*, *38*(4), 317–326. https://doi.org/10.1097/JCP.0000000000000898