

Management of hyperprolactinemia

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Case 1

- A 33-year-old lady is seen for delayed menses
- Married for 2 years
- No pregnancy despite attempts
- Prolactin 120 ng/mL (or mcg/L) (normal < 20)
- **How would you approach?**

Causes of hyperprolactinemia

1) Physiologic:

- Pregnancy
- Lactation
- Exercise
- Stress (physical or psychological)

Causes of hyperprolactinemia

2) Medications:

- Antipsychotics
- Antidepressants (SSRI)
- Anticonvulsants
- H₂ blockers
- Opiates
- Estrogens (oral contraceptives)
- Metoclopramide
- Methyldopa
- Domperidone
- Verapamil

Causes of hyperprolactinemia

3) Pituitary/hypothalamic disorders:

- Prolactinoma
- Pituitary/hypothalamic tumors or metastasis
- Granulomas (TB, Sarcoidosis)
- Surgery
- Trauma
- Lymphocytic hypophysitis

Causes of hyperprolactinemia

4) Systematic disorders:

- Hypothyroidism
- Chronic kidney disease
- Liver cirrhosis
- Chest wall (trauma, surgery, herpes zoster)
- Polycystic ovary syndrome
- Cranial irradiation

5) Idiopathic

Manifestations of hyperprolactinemia

- Oligomenorrhea
- Amenorrhea
- Infertility (can occur with normal menses)
- Galactorrhea
- Loss of libido, erectile dysfunction
- Gynecomastia
- Headaches, impaired vision
- Low bone mass

Evaluation of high prolactin:

History

- Menses (regular, frequency)
- Fertility
- Previous pregnancies
- Sexual desire in men
- Erectile function in men
- Headaches, visual symptoms, fatigue
- Symptoms of hypothyroidism
- Medications

Evaluation of high prolactin:

Examination

- Thyroid exam
- Signs of hypogonadism
- Visual field exam
- Chest wall exam
- Abdominal exam (if suspecting liver cirrhosis)

Evaluation of high prolactin:

Laboratory tests

- TSH
- Kidney function
- If normal TSH & Cr
 - Do MRI pituitary & hypothalamus with contrast

Evaluation of high prolactin

- How high is the prolactin level?
- > 200 ng/mL is suggestive of prolactinoma
- Mild increase (21 -40) can be due to: physical or emotional stress, meal, breast stimulation
- If mild increase, repeat the test **fasting**

If suspecting drug-induced hyperprolactinemia

- Prolactin levels is usually 25-100 ng
 - But may be >200 ng with antipsychotics
- History is important
 - **Relation of high prolactin to starting the medication**
 - **If any symptoms, did they start after the medication?**
- Stop the drug if possible
- Check prolactin after 3 days

If suspecting drug-induced hyperprolactinemia

- Consult psychiatrist before stopping antipsychotic medications
- If it is not possible to stop the medication:
 - Switch to another medication with a similar action
 - Check prolactin after 3 days
- If not possible to stop or change the medication:
 - Do MRI pituitary

Management of drug-induced hyperprolactinemia

- **If normal MRI:**
- **No symptoms:**
 - No treatment
- **If symptoms of hypogonadism:**
 - Estrogen for women
 - Testosterone for men
 - Dopamine agonists??

Evaluation of high prolactin: hypothyroidism

- Prolactin can be high with primary hypothyroidism
- Treat with thyroxine
- Once TSH is normal, repeat prolactin
- If prolactin is still high, do MRI pituitary

Evaluation of high prolactin: chronic kidney disease

- Due to increased prolactin secretion and decreased clearance
- Usually in CKD stage 4 & 5
- Can reach 10-fold normal
- If disturbing symptoms, other pituitary hormone abnormalities or mild degree of CKD:
 - Consider MRI (with no contrast)

Evaluation of high prolactin

- Do **NOT** start treatment before doing MRI

1) If MRI showed pituitary lesion:

- If prolactin is **> 200 ng**

- Suggestive of prolactinoma

- If prolactin **21-200 ng:**

- Still can be prolactinoma
- Or pituitary tumor

Evaluation of high prolactin

1) If MRI is **NORMAL**:

– Rule out other causes

– If no cause is found:

- **Idiopathic hyperprolactinemia**
- **It could be microadenoma not seen on MRI**
- Can try treatment if there are symptoms
- If no symptoms: no treatment is needed

Prolactinoma

- **Size < 1 cm = microprolactinoma**
- **Size \geq 1 cm = macroprolactinoma**

Initial assessment

- **Microprolactinoma**
- **If no symptoms:**
 - No need for treatment
 - Follow up
- **Macroprolactinoma**
- **Assess for hypopituitarism:**
 - Adrenal, thyroid, gonadal (see pituitary disorders)
- **Refer for visual field examination**

Hook effect: measurement of prolactin

- Serum prolactin level will be falsely low
- This is expected when prolactin level is 20 to 200 ng/mL in the presence of a macroadenoma
- This effect occurs when a very high prolactin saturates both the capture and signal antibodies used in immunoradiometric and chemiluminescent assays, preventing the binding of the two in a "sandwich."
- The artifact can be avoided by repeating the assay using a 1:100 dilution of serum
- It is uncommon

When to treat high prolactin?

- 1) Symptoms of hypogonadism (amenorrhea, oligomenorrhea, infertility, erectile dysfunction)
- 2) Neurologic symptoms due to the size of the tumor (impaired vision or headache)
- 3) Macroadenoma or if the tumor extends outside the sella, or elevates optic chiasm, or invades cavernous or sphenoid sinuses
- 4) Disturbing galactorrhea

Treatment of hyperprolactinemia

- Dopamine agonists:

1) Bromocriptine

- Low cost
- Start 1.25 mg at bedtime
- ↑ after 1 week to 1.25 mg bid (can go to 5 mg bid)
- After breakfast & after dinner
- Switch to cabergoline if intolerance or inadequate response
- Or use intravaginal form

Treatment of hyperprolactinemia

2) Cabergoline

- 1st choice
- More effective than bromocriptine
- Less side effects than bromocriptine
- Higher cost
- Start by 0.25 mg twice weekly (or 0.5 mg once/week)
- Taken with or without food
- If using > 2 mg/week, consider cardiac echo monitoring for valvular disease

Follow up after treatment of prolactinoma

- Advise the patient to **stop** treatment if she gets pregnant
- Check prolactin after 1-2 months
- Assess symptoms (menses, headaches,...)
- Assess for side effects (nausea, dizziness)

Follow up after treatment of prolactinoma

- Increase drug dose according to prolactin level
- Target is ↓ symptoms & normal prolactin level
- Decreasing tumor size is NOT the target

1) If normal prolactin:

- Continue same dose of medication
- Gonadal function may take **few months** to return

Follow up after treatment of prolactinoma

2) If prolactin is still high :

- Increase dose of medications
- Bromocriptine up to 5 mg bid
- Cabergoline 1.5 mg (2-3 times/week) (higher doses can be used)
- Continue same dose once prolactin is normal
- Some patients will have no symptoms with mildly high prolactin. Can keep same dose

Long term follow up of prolactinoma

- Once no symptoms
- Stable adenoma on MRI
- Check prolactin after 6 months then every year
- Stop treatment if pregnancy
- Repeat MRI:
 - After 6-12 months for microadenoma
 - After 3-6 months for macroadenoma
- Treatment for at least 2 years

Long term follow up of prolactinoma

- **If prolactin is normal for 1 year & no adenoma on MRI:**
 - Reduce dose of drug
 - Check prolactin every 3 months
- **If prolactin is normal and no adenoma on MRI for 2 years:**
 - Stop drug and monitor

Hyperprolactinemia: difficult cases

1) Dopamine agonist resistance:

- Inadequate response to treatment
- Failure to achieve a normal prolactin level and ↓ tumor size by 50% on maximally tolerated dopamine agonists
- Failure to restore fertility
- 25% with bromocriptine
- 10% with cabergoline
- More with macroprolactinomas
- Some have high prolactin with ↓ tumor size

2) Intolerance to both bromocriptine & cabergoline

Hyperprolactinemia: difficult cases

- **Drug resistance or intolerance**
- **For women:**
 - Clomiphene to help with pregnancy
 - Estrogen & progesterone (if pregnancy is not desired)
- **For men:**
 - hCG if attempting fertility
 - Testosterone if fertility is not desired
- Surgery is an option
- If tumor remains, consider radiation therapy

Prolactinoma: when to do surgery?

1. Intolerance to medical therapy
2. Inadequate response to medical therapy (resistance)
3. Pituitary apoplexy (hemorrhage) with neurological deficits

Follow up of idiopathic hyperprolactinemia

- High prolactin and normal MRI
- Some may have small adenomas not visible on MRI
- If no symptoms, no treatment is needed
- If symptoms, treat
- Check prolactin every 2-3 months
- Reduce drug dose to keep prolactin normal
- If normal prolactin for 2 years, try stopping the drug

Prolactinoma in pregnancy

- Stop treatment
- Those with microadenoma usually do fine
- Do not follow prolactin (it will be high)
- Generally, no need for MRI
- Patients with new symptoms (severe headaches or visual field abnormality): do formal visual field exam and MRI **without** contrast
- If ↑ growth, use bromocriptine

Galactorrhea with normal prolactin level

- Make sure it is clear or milky
- Green or black fluid usually represents milk (can be confirmed by staining for fat)
- Refer for evaluation if blood
- Cause is not known
- Reassurance. No treatment is needed
- If disturbing, can use small dose dopamine agonist (as cabergoline 0.25 mg twice/week)