Hyperprolactinemia

Justin Moore, MD
The Miraculous Lactation of St. Bernard

Bernard prayed before a statue of the Madonna, asking her, "Show yourself a mother" ("Monstra te esse Matrem"). The statue came to life and squirted milk from the breast onto the Saint's lips.

Artist: Alonso Cano, A.D. 1650

http://www.fisheaters.com/images/mariaclactans-miraculouslactationofstbernard.jpg
Learning points

• Pay attention to medications and possible mass effect in cases of galactorrhea/hyperprolactinemia
• Do not treat hyperprolactinemia unless the patient has amenorrhea, problematic galactorrhea, or a tumor that threatens the optic chiasm
• Do not check prolactin levels during pregnancy or immediately postpartum
Case One

- 24 year old female presents with secondary amenorrhea, galactorrhea
- No headaches, but some nausea
- Exam unremarkable with the exception of expressible galactorrhea
- TSH 1.0 uIU/mL, Prolactin 155 ng/mL, hCG undetectable
- MRI sella: 0.3 cm hypodense lesion in mid-pituitary
What is the most important question we can ask this woman?

A. What are your medications?
B. Do you have seizures or blackouts?
C. Are you wearing a new or different bra?
D. Have you had any recent chest trauma?
Medications

- Metoclopramide 10 mg TID
- Phenergan 25 mg QID prn
- Oxycodone 10 TID prn
Dopamine Deficiency

Defective Dopamine Transport

Dopamine Receptor Blockade

(Arterial flow)

Anterior pituitary

Posterior pituitary

GH, ACTH, TSH, FSH, LH, and prolactin

Vasopressin and oxytocin

(Arterial flow)

http://punker829.deviantart.com/art/The-Nipple-Man-2719968
Rule of thumb: expect a rise in prolactin of at least ~10 ng/ml for every 1 mm of tumor

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**log PRL µg/L**

(1000) (100) (10)

r = 0.779; p < 0.001

Y = 1.568 + 0.045x
Learning point #1

• Pay attention to dopamine antagonistic medications when evaluating galactorrhea
A 60-year-old woman was in an automobile collision. Findings from a CT scan performed in the emergency department suggested the possibility of a pituitary mass. A coronal section of a follow-up MRI is shown. The patient underwent menopause at age 42 years. She reported no headaches, visual problems, galactorrhea, or symptoms of acromegaly or Cushing disease.

Laboratory test results:
- TSH = 2.5 mIU/L
- Free T₄ = 1.3 ng/dL
- 8 AM cortisol = 18.2 μg/dL
- Estradiol = <32 pg/mL
- FSH = 3.0 IU/L
- IGF-1 = 136 ng/mL
- LH = 2.0 IU/L
- Prolactin = 30 ng/mL

Which one of the following management strategies would be the best next step?

A. Perform craniotomy for pituitary tumor removal
B. Perform conformal radiotherapy
C. Perform gamma knife radiosurgery
D. Treat with bromocriptine
E. Schedule periodic MRIs and hormone assessment
Y = 1.568 + 0.045x

r = 0.779; p < 0.001
Learning point #2

- Mass effect from non-functioning sella masses can cause modest (<100 ng/ml) elevations in prolactin.
Case Three

- 34 year old female presents with headaches, clear rhinorrhea, galactorrhea, and secondary amenorrhea
- Demonstrable visual field defect (homonymous hemianopsia) and spontaneous galactorrhea on exam
- MRI head: 4 cm isodense lesion arising from the sella and encasing the left carotid, with some mass effect on the optic chiasm
- Pituitary function testing:
  - Prolactin 8,642 ng/ml
  - TSH 1.0 ulU/mL, T4 8.1 ug/dL
  - FSH, E2 undetectable
Which of the following are potential presenting complaints of hyperprolactinemia?

A. Galactorrhea
B. Hypogonadism
C. Headaches
D. Visual field defects
E. All of the above
Learning point #3: Three reasons to treat a high prolactin:

1. Problematic galactorrhea
2. Hypogonadism/amenorrhea
3. Mass effect of a prolactinoma on the optic chiasm or other surrounding structures

4.2. We suggest that clinicians not treat asymptomatic patients harboring microprolactinomas with dopamine agonists (21 ISSN). We suggest treatment with a dopamine agonist or oral contraceptives in patients with microadenomas who have amenorrhea (21 ISSN).
What is the appropriate treatment for this patient’s prolactinoma?

A. Transsphenoidal surgery

B. Cabergoline 0.5 mg po three times weekly

C. Cyberknife

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Hypothalamic influence is primarily of inhibition (Prolactin Inhibiting Factor [PIF, aka dopamine])

- Bromocriptine
- Cabergoline

Diagram showing the anterior and posterior pituitary glands, GH, ACTH, TSH, FSH, LH, and prolactin. Dopamine and vasopressin and oxytocin are also illustrated.
Side Effects of Dopaminergics

Common:

- Nausea
- Headache
- Dizziness/postural hypotension
- Dyspepsia
- Nasal congestion

Less Common:

- Insomnia
- Raynaud’s
- Breast pain
- Depression
- Anxiety
- Psychosis
- Pulmonary fibrosis
- Constrictive pericarditis
- Dyskinesia
- Paresthesias
# Valvulopathy

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Case Patients (N=31)</th>
<th>Controls (N=663)</th>
<th>Adjusted Incidence-Rate Ratio (95% CI)(^\text{a})</th>
<th>P Value(^\text{f})</th>
</tr>
</thead>
<tbody>
<tr>
<td>No current or recent use of a dopamine agonist‡</td>
<td>19 (61)</td>
<td>530 (80)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Last daily dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pergolide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 mg</td>
<td>3 (10)</td>
<td>21 (3)</td>
<td>5.1 (1.3–20.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>&gt;3 mg</td>
<td>3 (10)</td>
<td>5 (1)</td>
<td>37.1 (5.1–270.6)</td>
<td></td>
</tr>
<tr>
<td>Cabergoline</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>≤3 mg</td>
<td>2 (7)</td>
<td>31 (5)</td>
<td>2.6 (0.5–12.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;3 mg</td>
<td>4 (13)</td>
<td>3 (0)</td>
<td>50.3 (6.6–381.4)</td>
<td></td>
</tr>
<tr>
<td>Cumulative duration of use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pergolide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>0</td>
<td>4 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6 mo</td>
<td>6 (19)</td>
<td>22 (3)</td>
<td>9.8 (2.9–33.1)</td>
<td></td>
</tr>
<tr>
<td>Cabergoline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>0</td>
<td>11 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6 mo</td>
<td>6 (19)</td>
<td>23 (4)</td>
<td>7.8 (2.2–27.4)</td>
<td></td>
</tr>
</tbody>
</table>

\(^\text{a}\) The incidence-rate ratio was adjusted for the use of other dopamine agonists or amantadine.

\(^\text{f}\) P values are for the comparison of the incidence-rate ratios of valvular regurgitation between the higher dose and lower dose of each drug.

\(^\text{‡}\) This is the reference category, defined as no use of a dopamine agonist during the 12 months before the index date.
## Table 3. Dopamine Receptor Agonist Drugs Associated With Impulse Control Disorder Events

<table>
<thead>
<tr>
<th>Drug</th>
<th>ICD Events, No.</th>
<th>All Events, No.</th>
<th>D₃ Selective</th>
<th>PRR³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole</td>
<td>410</td>
<td>2095</td>
<td>Yes</td>
<td>455.9</td>
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<tr>
<td>Ropinirole</td>
<td>188</td>
<td>2414</td>
<td>Yes</td>
<td>152.5</td>
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<tr>
<td>Cabergoline</td>
<td>56</td>
<td>1592</td>
<td>No</td>
<td>62.9</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>30</td>
<td>613</td>
<td>No</td>
<td>86.1</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>14</td>
<td>677</td>
<td>No</td>
<td>36.0</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>12</td>
<td>605</td>
<td>No</td>
<td>34.5</td>
</tr>
</tbody>
</table>
Serum Prolactin (ng/ml)

<table>
<thead>
<tr>
<th>Case</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3940</td>
<td>1730-5700</td>
</tr>
<tr>
<td>1 Month</td>
<td>2.2</td>
<td>1.7-3.0</td>
</tr>
<tr>
<td>3 Months</td>
<td>2.3</td>
<td>1.4-3.2</td>
</tr>
</tbody>
</table>

Case 2

| Baseline | 2630   | 1640-4940 |
| 6 Weeks  | 182    | 93-296    |

Time (hours)
Bromocriptine 2.5 mg three times per day.
PRL 2185 µg/L

PRL 43.9 µg/L
• Pt responds well to high-dose cabergoline, with a reduction in tumor size, improvement in visual fields, and normalization of prolactin (now 10 ng/ml) over one month
• She asks you when she can attempt pregnancy
At the patient’s first pregnancy test, which of the following should be done?

A. Obtain visual field testing
B. Obtain a gadolinium-enhanced MRI of the sella
C. Discontinue cabergoline
D. Start progesterone

6.1. We recommend that women with prolactinomas be instructed to discontinue dopamine agonist therapy as soon as they discover that they are pregnant (1\textbullet\textbullet\textbullet\textbullet). In selected patients with macroadenomas who become pregnant on dopaminergic therapy and who have not had prior surgical or radiation therapy, it may be prudent to continue dopaminergic therapy throughout the pregnancy, especially if the tumor is invasive or is abutting the optic chiasm (1\textbullet\textbullet\textbullet\textbullet).
Should she have a re-check of her prolactin during the pregnancy?

- Yes
- No

6.2. In pregnant patients with prolactinomas, we recommend against performing serum prolactin measurements during pregnancy (1 | ⊗⊗⊗⊗).

Obstet Gynecol 2009, PMID: 19935037
JCEM 2011, PMID: 21296991
So what do we do to follow her disease while pregnant?

6.3. We recommend **against** the use of routine pituitary MRI during pregnancy in patients with microadenomas or intrasellar macroadenomas unless there is clinical evidence for tumor growth such as visual field compromise (1 | ☐ ☐ ☐ ☐).
Pregnancy issues

- Safety of dopamine agonists
  - Probably associated with pregnancy loss and pre-term birth¹
- Tumor growth (25% or less)
- Lactation
  - Almost certainly safe²

¹ Arch Gynecol Obstet. 2014, PMID: 24664257
² J Clin Endocrinol Metab. 2013, PMID: 23162092
Learning points

• Hyperprolactinemia results from at least four mechanisms:
  o Decreased lactotroph sensitivity to dopamine (usually from drugs)
  o Stimulation of lactotrophs (usually from chest wall stimulation or suckling)
  o Decreased dopamine transport to the pituitary (“stalk effect”)
  o Prolactinoma

• So pay attention to medications and possible mass effect in cases of galactorrhea/hyperprolactinemia
Learning points

• Treatment of hyperprolactinemia should be targeted toward three goals:
  o Resumption of normal pituitary function
  o Preservation of vision
  o Cessation of problematic galactorrhea

• Do not check prolactin levels during pregnancy or immediately postpartum
Fontana delle Tette

Si trovava all’inizio del Calmaggiore e così l’ha descritta Matteo Sernagiotto (1810-1888):
"...vaga donna marmorea, sovr’ una conca marina con ambe mani stava spremendosi le turbide poppe, e due vivi zampilli d’acqua cristallina.

Perché industri congegnò di ruote, tolta al vicino Cagnano, offriano abbondante liquore le case e botteghe circostanti, alvise ponte pretore, in seguito a straordinaria cità, la costruiva nel 1550 e da quel tempo no alla caduta della Veneta Repubblica, di anno per tre giorni di seguito, a egliare l’ingresso del nuovo podestà, nella fontana gettava dall’una poppa retto vin bianco, e nero dall’altra, sollazzo del popolo esultante..."

Ricostruita nel 1989

Per favore, abbia la cura di queste bocce.