Prolactinomas: Medical versus Surgical Management

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Hyperprolactinemia: Pituitary Causes

1. Pituitary tumor
   a. Prolactinoma
   b. NFA - stalk effect can raise prolactin up to 150 mg/L
   c. Macroadenoma –
      a. Prolactin over 200 always prolactinoma
      b. Atypical macroprolactinoma can have a prolactin below 200;
      c. Microprolactinoma – prolactin can be as low as 50 mg/L

2. Hypothyroidism – increased TRH drives prolactin

3. Acromegaly
   a. hyperprolactinemia in 25% of acromegalics (co-secreters)

Macroprolactinemia

- Macroprolactinemia –
  - elevation of serum prolactin caused by predominance of high molecular mass
    circulating form of prolactin felt to be prolactin complexed with anti-prolactin
    immunoglobulins.
  - May present with symptoms of hyperprolactinemia
  - Diagnosed by chromatography
  - Found in 10% of hyperprolactinemic patients.
    - Mean serum prolactin 61 (range 20-663).
    - 78% of these patients have normal MRIs.

Source: Neurosurgery 34: 834, 1994

Prolactinomas - Diagnosis

- Prolactin level above normal on more than one occasion or
  single prolactin level over 70 mg/L
- MRI showing pituitary adenoma
- Correlation of tumor size with prolactin level to ensure that
  patient does not have NFA with stalk effect
- Large adenomas with slightly elevated prolactin can arise due to
  "hook effect", cystic prolactinomas, macroadenomas with stalk
  effect, or atypical prolactinomas

Source: JCEM 87: 581, 2002

"hook effect"
**Goals of treatment**
1. Normalize prolactin
2. Reduce tumor size
3. Prevent tumor growth
4. Alleviate symptoms of mass effect
5. Be able to wean off treatment once all of the above accomplished

**Prolactinomas – Medical Therapy**

**Prolactinomas Other Benefits of Treatment**

- Hyperprolactinemia is associated with:
  - Hyperlipidemia
  - Insulin resistance
- These improve after starting dopamine agonist therapy.

**Bromocriptine versus Cabergoline**

- A randomized multicenter trial involving 459 women showed that cabergoline is more effective and better tolerated than bromocriptine for prolactinomas.
- Normal prolactin levels were achieved in 59% of women treated with bromocriptine, while cabergoline restored normal prolactin in 83%.
- Amenorrhea persisted in 7% of women taking cabergoline versus 16% for bromocriptine.
- 3% stopped cabergoline due to drug intolerance versus 12% for bromocriptine.

**Withdrawal of dopamine agonists**

- Initial studies of dopamine agonist withdrawal included patients with normal prolactin regardless of whether tumor resolved on MRI. Cabergoline more effectively withdrawn than bromocriptine, with 0-44% rates of maintaining normal prolactin 2-48 months after bromocriptine withdrawal, compared to 10-69% rates of maintaining normal prolactin 3-60 months after cabergoline withdrawal.
  
  *Source: NEJM 349: 2023, 2003*

- **UCSF practice:** Patients with microprolactinomas on cabergoline who develop
  - (i) suppressed prolactin (below 5 µg/L), which usually occurs within a few months of starting medication;
  - (ii) no tumor visible on MRI (60% of treated patients); and
  - (iii) maintain this state for 2 years are considered for withdrawal of dopamine agonist.
Surgical indication # (%) out of 154 surgical cases 2001-2011

1. Patient choice 78 (51%)
2. Cyst/hemorrhage in tumor 23 (15%)
3. Medication not tolerated due to side effects. 18 (12%)
4. Can’t afford medication 14 (9%)
5. Dopamine agonist resistance 8 (5%)
6. Desired pregnancy 7 (5%)
7. Interaction with other meds 3 (2%)
8. Lack of rapid visual improvement with dopamine agonist 3 (2%)

Surgery for prolactinomas – UCSF indications

Resistance to Dopamine Agonists

- Dopamine agonist resistance tricky to define
- Resistance = failure of MRI and prolactin to normalize.
  - Resistance to maximal cabergoline far less common than resistance to bromocriptine, with 6-11% rates in literature.
  - Radiographic resistance where prolactin normalizes but not MRI is distinct and can be due to cyst in tumor or GH/ prolactin co-secreting tumor.

Surgery for Dopamine Agonist-Resistant Prolactinomas

Retrospective review of 71 prolactinomas operated on at a single center over 2 decades. Of indications for surgery, dopamine agonist resistance was not associated with significantly more recurrence than other indications for surgery.


Surgery for Dopamine Agonist-Resistant Prolactinomas

56 dopamine agonist-resistant prolactinoma patients operated on at 12 European Centers. Of 14 patients not cured by surgery, resulting prolactin reduction allowed significant cabergoline dose reduction.


UCSF experience – 6 dopamine agonist-resistant prolactinomas operated on with prolactin reduction from 2539 to 601, 50% dopamine agonist dose reduction.
Cost considerations

Cabergoline costs $110 (range $70-220) a month for 2 mg (starting dose), typical response requires at least doubling that dose.

Patient expense – as a Tier 2 drug, privately insured patients pay $25 per month for cabergoline. Medicaid often only covers bromocriptine (no out of pocket expense for patient) not cabergoline (patient covers full expense).

Cost-effectiveness comparative study from England suggest that cost differences between surgery (4925 Euro=$6779 US) and medicine equalize after 10 years of cabergoline at 1 mg/week (4534 Euro=$6241 US) when surgery is curative.

Analysis of UCSF data (actual hospital costs) revealed similar result – curative surgery ($22,790) equals 4 years of cabergoline ($20,249) or 8 years of bromocriptine ($22,289).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>Prolactin Reduction</th>
<th>Cost per 1% Prolactin Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>$39,959</td>
<td>93.4%</td>
<td>$428</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>$89,766</td>
<td>97.5%</td>
<td>$921</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>$158,038</td>
<td>97.1%</td>
<td>$1,621</td>
</tr>
</tbody>
</table>

Source: European Journal of Endocrinology 140: 43, 1999

UCSF data unpublished

### UCSF Prolactinoma Surgery – Pre-Treatment Data 2001-2011

<table>
<thead>
<tr>
<th></th>
<th>Prolactinomas</th>
<th>Prolactinomas (medical) analyzed cases</th>
<th>Hormone-negative adenomas (HNAs)</th>
<th>P, surgical prolactin vs. HNAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>154</td>
<td>128</td>
<td>1208</td>
<td>0.01</td>
</tr>
<tr>
<td>% female</td>
<td>66%</td>
<td>47%</td>
<td>43%</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean age</td>
<td>34</td>
<td>54</td>
<td>56</td>
<td>1.2X10^-12</td>
</tr>
<tr>
<td>Mean tumor size</td>
<td>1.5 cm</td>
<td>1.7 cm</td>
<td>2.5 cm</td>
<td>1.0X10^-5</td>
</tr>
<tr>
<td>% macroadenoma</td>
<td>63%</td>
<td>73%</td>
<td>93%</td>
<td>0.01</td>
</tr>
<tr>
<td>% with vision changes</td>
<td>19%</td>
<td>15%</td>
<td>66%</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>30.9</td>
<td>30.1</td>
<td>25.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values differing between prolactinomas undergoing surgery vs. hormone-negative adenomas undergoing surgery:

<table>
<thead>
<tr>
<th></th>
<th>Prolactinomas</th>
<th>Hormone Negative adenomas</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop prolactin</td>
<td>858 (range 40-53490)</td>
<td>18 (0.3-99.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Preop TSH</td>
<td>5.9</td>
<td>1.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Preop IGF-1</td>
<td>210</td>
<td>109</td>
<td>0.03</td>
</tr>
<tr>
<td>Irregular Menses</td>
<td>86%</td>
<td>24%</td>
<td>0.01</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>69%</td>
<td>18%</td>
<td>0.005</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>39%</td>
<td>5%</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>14%</td>
<td>39%</td>
<td>0.01</td>
</tr>
<tr>
<td>On dopamine agonist at surgery</td>
<td>56%</td>
<td>1%</td>
<td></td>
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</tbody>
</table>
### UCSF Prolactinoma Surgery – Postoperative Data

<table>
<thead>
<tr>
<th>Surgery after medical therapy</th>
<th>UCSF Prolactinoma Surgery – Postoperative Data</th>
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<tbody>
<tr>
<td></td>
<td>Immediate postoperative prolactin reliably predicts postop MRI findings</td>
</tr>
<tr>
<td></td>
<td>Sensitivity of Elevated Immediate Postop Prolactin for predicting residual on MRI</td>
</tr>
<tr>
<td></td>
<td>Specificity of Elevated Immediate Postop Prolactin for predicting residual on MRI</td>
</tr>
<tr>
<td>Percentage of patients with postoperative prolactin normalization as a function of preoperative prolactin in patients not on dopamine agonist therapy</td>
<td></td>
</tr>
<tr>
<td>% normal postop prolactin if preop prolactin &lt;300 vs. &gt;300</td>
<td>93% vs. 79%</td>
</tr>
<tr>
<td>% normal postop prolactin if preop prolactin &lt;600 vs. &gt;600</td>
<td>88% vs. 20%</td>
</tr>
</tbody>
</table>

**Success rates for prolactinoma surgery in literature:**

Microadenomas – 38-92%; Macroadenomas – 11-80%

**UCSF 1999 series** – 92% of microadenomas, 88% of non-invading macroadenomas, 80% of macroadenomas with suprasellar extension or sphenoid sinus invasion (*Neurosurgery* 44: 254).

### Surgery after medical therapy

- 24 consecutive resected prolactinomas at Johns Hopkins – more fibrous tumors noted in patients on preoperative bromocriptine

Source: *Pituitary* 14: 68-74, 2011

### Postoperative Data

<table>
<thead>
<tr>
<th>Prolactinomas</th>
<th>Hormone-negative adenomas</th>
<th>% GTR</th>
<th>% GTR (micro)</th>
<th>% GTR (macro)</th>
<th>Resolution of symptoms (%)</th>
<th>Postop prolactin</th>
<th>% normal postop prolactin</th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>88%</td>
<td>66%</td>
<td>&lt;0.05</td>
<td>94%</td>
<td>94%</td>
<td>0.4</td>
<td>80%</td>
<td>59%</td>
</tr>
<tr>
<td>67%</td>
<td>83%</td>
<td>&lt;0.05</td>
<td>276 (1-27900)</td>
<td>19</td>
<td>&lt;0.05</td>
<td>86%</td>
<td></td>
</tr>
</tbody>
</table>

**Source:** Pituitary 12: 158-164, 2009

- At UCSF, 253 prolactinoma patients undergoing surgery had greater reductions in prolactin levels and lower postop prolactin levels at long-term follow up and were less likely to require additional medical therapy if they were on preoperative bromocriptine (n=77) versus if they had never been exposed to preoperative dopamine agonists (n=176).
Surgery after medical therapy

UCSF results – improved postoperative control in patients on preoperative dopamine agonists.

Source: Pituitary 12: 158-164, 2009

Long-term results after prolactinoma failure to surgically cure

UCSF - 18 Patients
Mean preoperative prolactin = 1300
14 macroadenomas / 4 microadenomas
Mean preoperative tumor size = 2.3 cm
Mean postoperative prolactin = 541
6 patients with residual in cavernous sinus treated with radiosurgery due to intolerance of medications, with 50% cure rate at 2 years
12 patients with larger residual – 3 treated with external beam radiation therapy, 9 treated with dopamine agonists

Durability of Remission after Prolactinoma Surgery

UCSF experience – of 103 cured patients with follow-up, 3 (3%) recurred. Time to recurrence averaged 3.1 years (range=2.9-3.5 years). Recurrences too few to identify risk factors.

87 consecutive surgical prolactinomas operated on at a center in China. Of cured patients, 5-year recurrence rate was 22%


Gamma knife for prolactinomas

Limited experience because medical management is so effective, often in place of transsphenoidal surgery
Retrospective review of 23 patients with prolactinomas that underwent gamma knife radiosurgery at UVA 1990-2003 after failing medical and surgical treatment
Clinical remission in 26% an average of 24 months after radiosurgery.
No dopamine agonist at the time of radiosurgery and pre-gamma knife tumor volume predicted remission.

Source: Neurosurgery 59: 255, 2006
A 38-year-old woman with amenorrhea and visual symptoms. Prolactin = 85 ng/ml. MRI (A and B) showed a cystic lesion with suprasellar extension and chiasm compression. Prolactin normalized to 14.1 ng/ml with bromocriptine, but tumor did not respond. She underwent transsphenoidal complete resection of tumor.

Pathology = prolactinoma.

Illustrative case

Illustrative case #2

72 year old female presents with right eye vision loss. MRI with 11X6X12 mm right sellar lesion invading cavernous sinus. Prolactin = 107.4 mg/L, IGF-1 = 130 ng/mL. After 6 months of cabergoline, prolactin = 9.5 mg/L but no regression of lesion and persistence of the right vision loss. Tumor surgically resected and co-stained for GH and prolactin.

Illustrative case

Conclusions

- While dopamine agonists have been invaluable in the management of prolactinomas, surgery still plays a role in their management.
- UCSF practice for newly diagnosed patients – dual consultations with endocrine and neurosurgery if neurosurgeons deem cure possible based in size, invasion, and preop prolactin. Surgery particularly considered if diagnosis unclear or cystic/hemorrhagic lesion.
- Surgery also offered for patients intolerant of medical therapy, or failure of medical therapy. The reasons these patients are unable to be treated medically will often lead to a need for radiotherapy or radiosurgery if there is residual after surgery.
- Aside from the considerations above, curative surgery may be more cost-effective in the long-run.

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