Treating Cystic Prolactinomas with Dopamine Agonists: Partial Cabergoline Resistance and Considering Dose Reduction

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Objectives

- To utilize this case as a basis to consider dopamine agonist dose reduction when managing partially resistant cystic prolactinomas.
- To analyze the existing evidence and assumptions about the effectiveness of dopamine agonists in the management cystic prolactinomas.
Our Case

A 26 year old male presented to his primary care physician with the chief complaint of erectile dysfunction and decreased libido for the past 8 months.

- Difficulty in maintaining an erection.
- Absence of morning or spontaneous erections.
- Has nocturnal emissions about every month.
- No apparent issues in the relationship with his girlfriend who is generally supportive.
Associated Symptoms

- Weight gain of 40 pounds over the past 4 years.
- Fatigue/Decreased Energy.
- Mild intermittent headaches.
Pertinent Negatives

- Denies dizziness or generalized weakness.
- Denies heat intolerance, cold intolerance, polydipsia, or polyphagia.
- Denies changes in vision or visual disturbances.
- Denies abdominal pain, nausea, vomiting, or change in bowel habits.
- Denies changes in urination.
- Denies change in body/facial hair or changes in skin tone.
Other Histories

- No known medical history.
- No history of surgeries.
- Family history: diabetes mellitus in grandparents, no history of tumors including pituitary, no history of thyroid problems.
- Social history: No tobacco, alcohol, or recreational/illicit drug use.
- Not on any medications or supplements, including over the counter medications.
Vitals

- Height: 5’ 10”
- Weight: 90 kg
- BMI: 29
- Blood Pressure: 112/72 mmHg
- Pulse: 66
- Respiratory Rate: 16
- Temperature: 36 F
Physical Examination

- Constitutional: Overweight.
- HEENT: Normocephalic, no thyromegaly, no thyroid nodules.
- Genitourinary: No penile abnormalities, Testes 25-30ml bilaterally, non tender, no scrotal masses appreciated.
- Integumentary: No hyper or hypopigmentation, pubic hair normally distributed.
- Psychiatric: Appropriate mood and affect.
- Heart, Lung, Abdominal, and Neurological exam unremarkable.
Workup

- FSH: 0.6 mIU/mL
- LH: 1.0 mIU/mL
- Testosterone: 67 ng/dL
- Estradiol: 22 pg/mL
- TSH: 0.965 mIU/mL
- Free Thyroxine: 0.8 ng/dL

- Prolactin: 748 ng/mL
- Insulin like Growth Factor: 176 ng/mL
- Cortisol: 8.5 µg/dL (noon)
- ACTH: 58 pg/mL
First MRI
First MRI
A 2.0 X 2.0 x 1.8 cm mass is noted in the sella, that is isointense on T1-weighted images and demonstrates increased T2 signal.

This mass demonstrates homogeneous enhancement in the post contrast images, with remodeling of the floor of the sella.

The mass abuts the optic chiasm, and is contacting less than 25% of the cavernous portion of the right internal carotid artery.

The pituitary stalk is elevated and displaced posteriorly by the mass.

The size, position and signal intensity of the optic chiasm are normal.

The ventricular size and brain volume are normal.

The morphology of the midline structures and the cervicomedullary junction are normal.

**IMPRESSSION:**
A 2.0 cm pituitary mass, likely macroadenoma, is contacting the optic chiasm without elevation. This lesion is abutting the right cavernous internal carotid artery.
Initial Management and Response

- Patient was started on 0.5 mg cabergoline twice weekly following elevated prolactin level.
- Prolactin reduced to 43 ng/mL after merely two doses.
- Cabergoline was being tolerated well.

At two months patient reported:
- Improved energy and libido.
- Decreased headache intensity and frequency.
- Intermittent tingling/numbness in fingers and toes.
- Visual fields remained unaffected.
Second MRI

At Five Months
Second MRI

At Five Months
Radiology Report

- There is a focal T2 hyperintense mass within the right aspect of the pituitary gland. This mass exhibits some internal areas of heterogeneous enhancement. The mass itself measures 1.4 x 1.0 x 1.3 cm (TV, CC, AP), and the overall pituitary gland 1.6 x 1.0 x 1.6 cm (TV, CC, AP).
- There is partial effacement of the suprasellar cistern, however, no significant suprasellar extension of the pituitary gland is present, and the optic chiasm is unencumbered.
- There is slight leftward deviation of the pituitary infundibulum, which is of normal thickness and exhibits normal enhancement.

**IMPRESSION:**
1.4 x 1.0 x 1.3 cm macroadenoma within the right aspect of the pituitary gland. Enhancing lip of tissue extends along the medial and cephalad margin of the right cavernous ICA, which exhibits a normal flow void. No significant suprasellar extension is present and there is no mass effect upon the optic chiasm.
Till Thirteenth Month

Cabergoline dose was increased gradually given the suboptimal response of prolactin level, even with adequate dosing prolactin level failed to fall below the upper limit of normal 17.7 in the first year of treatment.

<table>
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<th>0.25</th>
<th>4</th>
<th>9</th>
<th>10</th>
<th>12</th>
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<tr>
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<td>42.8</td>
<td>29.7</td>
<td>31.5</td>
<td>24.7</td>
<td>20.7</td>
<td>20.4</td>
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<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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Third MRI
At Fourteen Months
Third MRI

At Fourteen Months
Fourteen Month Follow Up

- Prolactin 20.4
- Cabergoline increased to 2 mg three times a week. Total 6 mg per week.
- Baseline EKG and Echocardiogram ordered due to increased dose of cabergoline.
- Patient had bradycardia of 50s, mild tricuspid regurgitation, pulmonic valve regurgitation, and borderline right ventricular dilatation. He was referred to Cardiology for monitoring.
The Last Dose Increase

- The cabergoline dose was then increased to 7 mg a week at month 22 as prolactin stayed at upper limit of normal with 6 mg per week.
- The 7 mg per week dose was continued for two years to maintain a prolactin below 10.

<table>
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<th>Month</th>
<th>14</th>
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<th>20</th>
<th>22</th>
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<td>9.4</td>
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At 7 mg per Week, Month 22 to 49

- Minimal if any reduction in size on 7 mg per week cabergoline dose, despite two years of continuation at the same dose.
- The patient was offered the option of surgery, however he persisted to continue with medical therapy.

29 Months 35 Months 41 Months
A Trial of Dose Reduction

- At month 52 and 64 dose was reduced to 5 mg per week then 3 mg per week respectively.
- Despite the dose reduction, there was a reduction in the size of the prolactinoma with the cystic portion becoming more apparent.
- Additionally an acceptable prolactin level was maintained.

<table>
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<th>Dose Level</th>
<th>Duration</th>
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<td>7 mg per week</td>
<td>41 Months</td>
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<tr>
<td>5 mg per week</td>
<td>56 Months</td>
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<tr>
<td>3 mg per week</td>
<td>67 Months</td>
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Cabergoline Dose Graphed with Prolactin Level
Discussion

- Cystic prolactinomas are prolactinomas that harbor cystic regions.
- The cystic component usually occupies fifty percent or more of the mass.
- Cyst formation is thought to occur due the resolution of a preceding hemorrhage into the adenoma, or by mere necrosis of the tumor.
- Cyst formation can occur spontaneously or in conjunction with other factors such as radiation therapy, trauma and use of anticoagulants [3].
Prior Assumption

- Management of cystic prolactinomas was not discussed in the 2011 Endocrine Society clinical practice guidelines [6].
- According to the Pituitary Society Guidelines (2006), surgery should be considered as a treatment for cystic macroadenomas causing neurological symptoms [5].
- It was generally assumed that, while the solid component of the tumor usually maintains responsiveness to dopamine agonists, such agents are ineffective in reducing cystic tumor mass due to the absence of dopamine receptors in the cystic portion of the tumor [2]. This assumption however lacks evidence.
Advantages to Surgery

- Transphenoidal resection technically easier for cystic tumors than for solid tumors and can result in rapid relief of the pressure on the optic chiasm.
- Surgery should be considered for cystic prolactinomas that are resistant to dopamine agonist therapy and in cases of intolerance to long-term medical therapy.
- Histopathological diagnosis can be obtained when prolactin level is equivocal and the diagnosis is not straightforward.
Evidence / Cases

Faje, et. al, Dopamine Agonists Can Reduce Cystic Prolactinomas, *The Journal of Clinical Endocrinology & Metabolism*, October 2016

A retrospective review of 30 adults with cystic prolactinomas treated at Massachusetts General Hospital, conclusion was: “Significant cyst reduction occurred in the majority of patients treated with DAs, including those with larger lesions and chiasm compression. This study is the first formal analysis of cyst reduction with DAs in patients with cystic prolactinomas, and contrary to long-held assumptions, our results suggest that medical therapy may be effective in many such patients.”

Nakhleh et. al, Management of cystic prolactinomas: a review, *Pituitary*, August 2018

A literature review of PubMed cases and case series about the approach to managing cystic prolactinomas, conclusion: “Recent studies suggest that dopamine agonist therapy may be an effective and safe treatment option in a considerable portion of patients with cystic prolactinomas. We suggest that dopamine agonists should be considered as a first-line therapy for cystic prolactinoma in the absence of indications for early surgical intervention.”


