CLINICAL PRACTICE

Prolactinomas

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 42-year-old man presents with decreased libido, erectile dysfunction, and headaches. He reports no weight change, gynecomastia, fatigue, or other symptoms. He takes no medications. Testicular size is decreased on examination. His prolactin level is 648 μg per liter (normal value, <15). Magnetic resonance imaging (MRI) reveals a sellar mass (2.5 by 1.5 by 2.0 cm) that is 5 mm below the optic chiasm and that extends bilaterally into the cavernous sinuses. What are the diagnostic and therapeutic considerations?

THE CLINICAL PROBLEM

Prolactinomas are the most common type of secretory pituitary tumor. Typically benign, they are classified according to size; microadenomas are less than 10 mm and macroadenomas 10 mm or more. Serum levels of prolactin in patients with prolactinomas are usually proportional to the tumor mass, and prolactin levels above 250 μg per liter are common in patients with macroprolactinomas; levels can exceed 10,000 μg per liter. Pituitary microadenomas are found in 10.9% of autopsies, and 44% of these microadenomas are prolactinomas.[1] Although they are rarely hereditary, prolactinomas can occur as part of the multiple endocrine neoplasia type 1 syndrome. No risk factors have been identified for sporadic prolactinomas. Although it has been hypothesized that oral contraceptives might increase the risk, their use has not been associated with an increased likelihood of prolactinoma development.[2]

Clinical symptoms and signs of hyperprolactinemia in women include oligoamenorrhea, infertility, and galactorrhea. Restoration of ovulatory menstrual periods when pulsatile gonadotropin-releasing hormone (GnRH) is administered in women with hyperprolactinemia confirms the presence of abnormalities in GnRH secretion in these patients.[3] In women with hyperprolactinemia who continue to have menses, luteal-phase abnormalities can lead to infertility. Estrogen deficiency in amenorrheic women with untreated prolactinomas causes low bone mass and is associated with an increased risk of fracture, whereas bone density is preserved in women with hyperprolactinemia who have regular menses.[4,5] Large prolactinomas can also cause gonadotropin insufficiency because of mass effect (compression of normal gonadotrophs). In men, hyperprolactinemia may lead to hypogonadism, decreased libido, erectile dysfunction, infertility, gynecomastia, and, in rare instances, galactorrhea. Decreased bone mass[6] and anemia can result from testosterone deficiency. In contrast with women, who usually present with microadenomas, most men present with macroadenomas, often with headache, visual symptoms, or both, in addition to hypogonadism.[7] The larger tumor size in men presumably reflects diagnostic delay, although there may be sex-specific differences in biologic features of the tumors. Although rare, prolactinomas may occur in children, typically with mass effect, pubertal delay, or both.[8]

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STRATEGIES AND EVIDENCE

EVALUATION

The evaluation of hyperprolactinemia begins with consideration of physiologic causes, including pregnancy in women of childbearing age. Interpretation of postpartum hyperprolactinemia depends on how much time has passed since delivery and whether the woman is nursing. Prolactin levels normalize within approximately 6 months after delivery in nursing mothers and within weeks in non-nursing mothers.[9] Prolactin elevations also occur in patients with renal or hepatic failure (because of reduced prolactin clearance), primary hypothyroidism, or neurogenic stimulation, such as that which occurs with chest-wall injury or transiently with nipple stimulation. Pituitary tumors other than prolactinomas may secrete prolactin in addition to other hormones. Secretion of prolactin is under tonic inhibitory control by hypothalamic dopamine; levels of prolactin can be increased in the presence of tumors other than pituitary adenomas, inflammatory disorders such as lymphocytic hypophysitis, cysts (e.g., Rathke's cysts), which disrupt dopamine transport down the pituitary stalk, or medications that interfere with normal secretion of hypothalamic dopamine. Medications causing elevated prolactin levels include antidepressants and antipsychotic agents (risperidone, in particular),[10] other dopaminergic blockers (e.g., metoclopramide), some antihypertensive agents, opiates, and H_2-receptor blockers. Elevations in prolactin levels that result from stalk compression rarely exceed 150 μg per liter, but the use of antipsychotic agents or metoclopramide can increase prolactin levels to more than 200 μg per liter. Clinical manifestations of drug-induced hyperprolactinemia are similar to those of prolactinomas, except for tumor mass effects.[11,12]

Symptoms of hyperprolactinemia do not correlate well with prolactin levels, although most patients whose prolactin levels are above 150 μg per liter for any reason have associated symptoms. Macroprolactin, a complex of prolactin and an IgG antibody, can cause spurious hyperprolactinemia because of delayed clearance, but such occurrences are rare.[13]

Table 1. Indications for Therapy in Patients with Prolactinomas.

Macroadenoma
Enlarging microadenoma
Infertility
Bothersome galactorrhea
Gynecomastia
Testosterone deficiency
Oligomenorrhea or amenorrhea
Acne and hirsutism

LABORATORY TESTING AND IMAGING

After rechecking an elevated prolactin level for confirmation, pregnancy should be ruled out in women of childbearing age, levels of thyrotropin and free T_4 measured, and renal and hepatic function assessed. Once other possible causes of an elevated prolactin level have been ruled out, MRI of the head should be performed, with the use of contrast material, and pituitary images obtained; MRI is indicated even in cases of mild hyperprolactinemia to determine tumor size and to rule out the presence of other sellar and stalk lesions. Some prolactin assays greatly underestimate extremely high levels of the hormone (e.g., high levels of antigen interfere with immunoradiometric assays), and because of this so-called hook effect, diluted serum samples should be obtained in patients with MRI findings that are consistent with a pituitary macroadenoma and a mildly elevated prolactin level.[14]

Testing of pituitary function is usually unnecessary in patients with microadenomas because pituitary function is typically normal in such patients. In amenorrheic women, serum levels of follicle-stimulating hormone should be measured to rule out primary ovarian failure, and serum testosterone levels should be assessed in men with hyperprolactinemia; infertility (in patients desiring fertility) is an indication for therapy. Bone density should be evaluated in patients with hypogonadism. Patients with macroadenomas that are adjacent to the optic chiasm or are compressing it require visual-field testing, since visual compromise necessitates rapid treatment.

MANAGEMENT

In contrast to macroadenomas, for which therapy is routinely indicated, microadenomas do not always require treatment. Indications for treatment are listed in Table 1. For patients with microadenomas who do not have these indications, symptoms and prolactin levels can be monitored, and MRI can be used to follow the size of the tumor. Several small retrospective and prospective series have shown that the risk of microadenoma en-

Table 2. Dose Recommendations and Side-Effect Profiles for Dopamine Agonists Approved for Use in the United States.

Medication	Dose*	Side Effects of Both Drugs†
Bromocriptine	Initial: 0.625 to 1.25 mg daily; usual range for maintenance dose: 2.5–10.0 mg daily	Common: nausea, headaches, dizziness (postural hypotension), nasal congestion, constipation Infrequent: fatigue, anxiety, depression, alcohol intolerance
Cabergoline	Initial: 0.25–0.5 mg weekly; usual range for maintenance dose: 0.25–3.0 mg weekly	Rare: cold-sensitive vasospasm, psychosis Possible: cardiac-valve abnormalities

* Doses are increased until limited by side effects, with prolactin levels generally measured every 4 weeks for patients receiving bromocriptine and every 8 weeks for patients receiving cabergoline, so that the lowest effective dose is used. Doses are increased until prolactin levels are within the normal range, gonadal function returns, or a plateau effect is reached, depending on the indication for treatment. A typical dose-adjustment strategy involves increasing the daily dose on a weekly basis, with the daily dose of bromocriptine increased by 1.25 to 2.5 mg and the weekly dose of cabergoline increased by 0.25 to 0.5 mg. Symptoms of mass effect or visual loss require more rapid escalation (e.g., doubling of the dose every 3 to 5 days, until limited by side effects) until an optimal dose is reached. Maximum doses usually do not exceed 10 mg of bromocriptine per day and 3 mg of cabergoline per week.

† Side effects may occur with all dopamine agonists but are less common with cabergoline than with bromocriptine and can be minimized by starting with a very low dose and directing the patient to take the drug with food before going to sleep at night. Bromocriptine can be prescribed in daily divided doses and cabergoline in weekly divided doses as needed to improve tolerability.

largement in untreated patients is low; small increases occur in approximately 20% of patients over time.[15-17] Because prolactin levels usually, but not always, correspond to changes in tumor size, both prolactin levels and tumor size (assessed with the use of MRI) should be checked routinely (e.g., once a year for 3 years and then every 2 years if the patient's condition is stable, although data regarding optimal follow-up intervals are lacking). Spontaneous resolution of hyperprolactinemia occurs in some untreated patients and appears to be particularly likely in women who are eumenorrheic at the time of presentation[16,17] and in postmenopausal women[18]; consequently, treatment of postmenopausal women is warranted only if a macroadenoma is present or there are symptoms or signs due to mass effect or there is troublesome galactorrhea. In women with microadenomas who want to use oral contraceptives for birth control or who have side effects from dopamine agonists, oral contraceptives are often used. In one study of 38 amenorrheic women treated for 2 to 8 years with hormone-replacement therapy or oral contraceptives, tumor enlargement did not occur.[19]

Dopamine Agonists

General Guidelines

Dopamine agonists are the primary therapy for both microadenomas that require treatment and macroprolactinomas. They rapidly normalize prolactin levels, restore reproductive function, reverse galactorrhea, and decrease tumor size in most patients.[20] Dopamine agonists (Table 2) include bromocriptine and cabergoline (both ergot derivatives) and quinagolide (not approved for use in the United States). Although all dopamine agonists lower prolactin levels, in a double-blind, randomized trial involving 459 women, cabergoline had fewer side effects and was more effective at normalizing prolactin levels as compared with bromocriptine; prolactin levels normalized in 83% of the patients treated with cabergoline versus 59% of those treated with bromocriptine.[21] Restoration of reproductive function with these agents improves bone density[22] in both sexes.

If levels of reproductive hormones remain low in men and premenopausal women with persistent hyperprolactinemia even after maximum treatment with dopamine agonists, gonadal steroid–replacement therapy may be required. Infrequently (usually in patients with large prolactinomas and permanent hypogonadism that is the result of gonadotroph destruction), gonadal steroid–replacement therapy may be required even when prolactin levels return to normal.

In patients with macroadenomas, additional goals of treatment are to decrease or stabilize the tumor mass and to prevent neurologic complications, including headaches and cranial-nerve compression syndromes. Dopamine agonists decrease tumor mass in the majority of patients and are used as primary therapy[23,24]; tumor shrinkage (Fig. 1) and visual-field improvement (Fig. 2) may occur within weeks. Bromocriptine and cabergoline have been studied most extensively in this regard, although their effects on tumor shrinkage have not been directly compared in randomized trials. In some patients with large macroadenomas and very high serum levels of prolactin, the prolactin levels may decline markedly but not normalize. If the tumor size is stable,

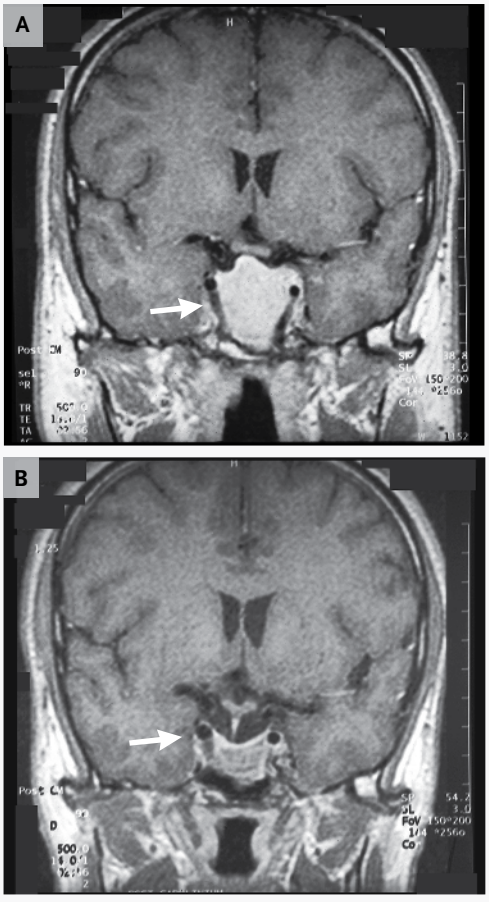

Figure 1. MRI Scans Showing Tumor Shrinkage after Treatment with a Dopamine Agonist in a Patient with a Macroprolactinoma.

Gadolinium-enhanced MRI scans obtained before dopamine agonist therapy, showing a large pituitary mass (Panel A, arrow) and after 1 year of treatment, with marked reduction of the mass (Panel B, arrow).

without symptoms of mass effect, and hormone deficiencies are treated, there is no evidence that continued elevation of prolactin levels is harmful. In patients with clinically significant visual-field compromise, doses are escalated more rapidly, with monitoring of visual fields at intervals of 2 to 4 weeks. If visual fields do not normalize and MRI shows continued chiasmal compression, neurosurgical intervention is usually indicated. If chiasmal decompression is revealed on MRI but visual-field abnormalities persist, recovery may take longer or visual loss may be permanent. Recovery of vision is highly variable and depends on many factors, including whether there is optic-nerve atrophy. For cases in which anterior pituitary hormone function is compromised, recovery may occur with tumor shrinkage. In rare instances, rapid shrinkage of large tumors results in a cerebrospinal fluid leak that requires surgical repair. A minority of tumors show a relatively modest response despite increasing doses of medication. In these cases, resistance to therapy has been attributed to a reduced density of dopamine receptors on the tumor, and a change in medication (e.g., from bromocriptine to cabergoline or quinagolide) may lead to improvement.[25,26]

Therapy should be initiated at a low dose, which should be increased slowly to minimize side effects; gastrointestinal symptoms and orthostatic hypotension are common (Table 2). Also of concern is a possible association between long-term treatment with dopamine agonists and cardiac-valve abnormalities, although data from long-term, prospective, controlled studies are lacking. An association between ergot alkaloid use and an increased risk of cardiac-valve disease was reported in the early 1990s,[27] and two studies published in 2007 showed an increased risk of cardiac-valve regurgitation in patients with Parkinson's disease who had been treated with high doses of cabergoline or pergolide; the risk was not increased among patients treated with other dopamine agonists.[28,29] Higher doses and a longer duration of therapy were associated with a higher risk of valvulopathy. The mechanism of its development has been postulated to be $5HT_{2B}$-receptor stimulation leading to fibromyoblast proliferation.[30] Whereas the dopamine agonist doses typically used for prolactinomas are much lower than those used for Parkinson's disease, many patients with prolactinomas are treated for decades, raising concern regarding this risk. Most studies have shown no association between use of dopamine agonists (including ergot derivatives) and cardiac-valve disease in patients with prolactinomas.[31,32] However, a cross-sectional study showed a higher rate of asymptomatic tricuspid regurgitation among cabergoline-treated patients than among untreated patients with newly diagnosed prolactinomas or normal controls.[33,34] The U.K. Department of Health has issued an advisory regarding the use of cabergoline, specifically regarding patients with previous valve problems; no such advisory has been issued in the United States.

Duration of Therapy

The appropriate duration of dopamine agonist therapy in a given patient is uncertain. In a retrospective series of 131 patients treated with bromocriptine for a median of 47 months, sustained normoprolactinemia was reported in 21% at a median follow-up of 44 months after treatment had been withdrawn.[35] In a large, prospective cohort study of the effects of cabergoline withdrawal[36] in patients who met specific criteria during treatment (including a normal serum prolactin level and no visible tumor or a decrease in tumor size of at least 50% from baseline and a distance of at least 5 mm between the tumor and the optic chiasm, without extrasellar invasion), rates of recurrent hyperprolactinemia were 30% among patients with microadenomas and 36% among those with macroadenomas after a median of 12 and 18 months, respectively. However, a higher recurrence rate (approximately 50%) was subsequently reported by this group in a larger series of patients with macroadenomas who were followed for up to 96 months.[37] In another study, a recurrence rate of 64% was reported 1 year after discontinuation of the dopamine agonist among patients with microadenomas.[38] A meta-analysis of 19 studies involving 743 patients noted sustained normoprolactinemia in a minority of patients (21%) after withdrawal of the dopamine agonist.[39] Patients with at least 2 years of therapy before its withdrawal and no demonstrable tumor visible on MRI had the highest probability of consistently normal prolactin levels.

The mechanism underlying sustained remission may be related to tumor necrosis and to the fibrotic changes that can occur in response to long-term dopamine agonist therapy.[40] Ultimately, withdrawal of therapy appears to be appropriate only for a subgroup of patients. For many patients with macroprolactinomas who have sellar or extrasellar tumors or persistent hyperprolactinemia during therapy, cessation of treatment is inadvisable.

Surgical and Radiation Therapy

Given the efficacy of medical therapy, only a small minority of patients with prolactinomas require transsphenoidal surgery or radiation therapy. Indications for surgery are listed in Table 3. Surgical cure rates, which are highly dependent on surgical skill and tumor anatomy, approach 80 to 90% for microadenomas but are less than 50% for macroadenomas. When surgery is performed by neurosurgeons who have done many of these procedures, the associated mortality rate is extremely low (0.2%), and immediate complications (including cerebrospinal fluid leak, which occurs at a rate of 1.4%) are infrequent.[41] Tumor recurrence is uncommon after surgery for microadenomas,[42] but recurrent hyperprolactinemia is reported in up to 80% of patients with macroadenomas.[43] Radiation therapy is occasionally used in patients with large lesions who are not candidates for further surgery and who have side effects from or do not have a response to dopamine agonist therapy.[44]

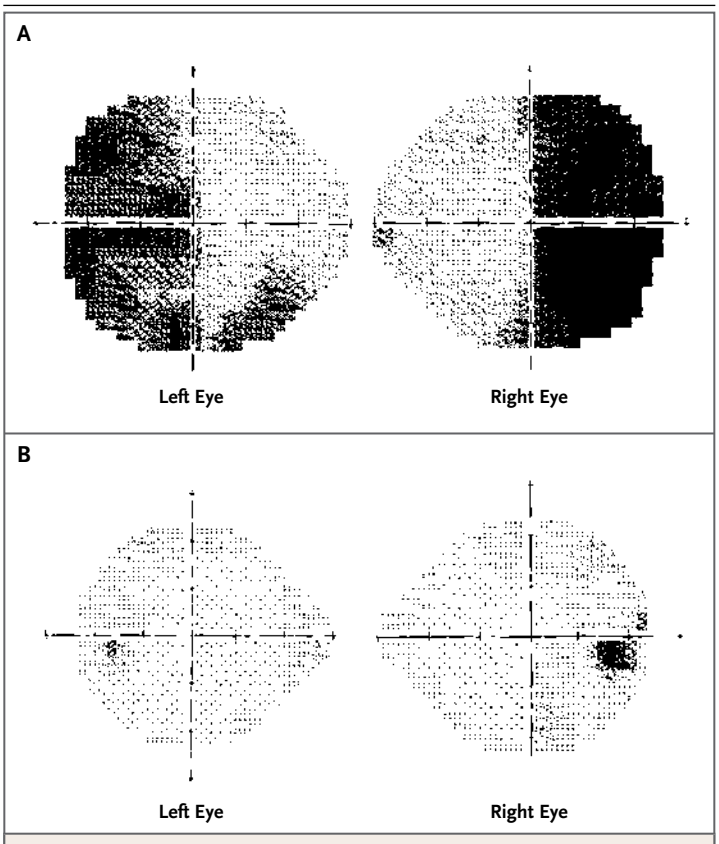

Figure 2. Automated Visual-Field Tests Showing Improvement in Visual Fields after Treatment with a Dopamine Agonist in a Patient with a Macroprolactinoma and Chiasmal Compression.

Visual-field testing shows the loss of visual fields (black areas) before initiation of dopamine agonist therapy (Panel A) and normalization (white areas) after 2 months of treatment (Panel B).

Monitoring during Pregnancy

A normal serum prolactin level is the goal in treating women who desire fertility, although some women with elevated prolactin levels do

Table 3. Indications for Neurosurgery in Patients with Prolactinomas.

Increasing tumor size despite optimal medical therapy
Pituitary apoplexy
Inability to tolerate dopamine agonist therapy
Dopamine agonist–resistant macroadenoma
Dopamine agonist–resistant microadenoma in a woman seeking fertility, if ovulation induction is not appropriate
Persistent chiasmal compression despite optimal medical therapy
Medically unresponsive cystic prolactinoma
In women seeking fertility, macroadenoma in close proximity to optic chiasm despite optimal medical therapy (prepregnancy debulking recommended)
Cerebrospinal fluid leak during administration of dopamine agonist
Macroadenoma in a patient with a psychiatric condition for which dopamine agonists are contraindicated

become pregnant. Because rising estrogen levels during pregnancy cause increased prolactin levels and lactotroph hyperplasia, pregnancy may pose risks for women with prolactinomas. Whereas the incidence of clinically significant tumor enlargement during pregnancy is less than 3% in women with microadenomas, it is approximately 30% in women with macroadenomas.[45] During normal pregnancy, there is a marked increase in prolactin levels and pituitary size. Routine monitoring of prolactin levels and MRI should not be performed during pregnancy in patients with prolactinomas, because a decision to treat is based on symptoms and signs and not on prolactin level or MRI findings alone. However, in women with macroprolactinomas, visual-field testing is recommended in each trimester — or more frequently, depending on whether the tumor showed evidence of suprasellar extension (e.g., was near the optic chiasm) before pregnancy. If visual-field abnormalities or other neurologic symptoms develop, a limited MRI study, focusing on the pituitary and without the use of contrast material, is recommended.

Dopamine agonists are not approved for use during pregnancy and should be discontinued once pregnancy occurs. However, reinitiation of treatment with bromocriptine is recommended if neurologic findings attributable to tumor enlargement occur during pregnancy. Data from more than 2500 pregnancies suggest that bromocriptine is not associated with an increased risk of birth defects.[46] Experience with the use of cabergoline in pregnancy is more limited, but the available data, on 380 pregnancies, are reassuring.[47]

In most women with prolactinomas, hyperprolactinemia persists after delivery, although spontaneous resumption of menses and remission of hyperprolactinemia can occur.[48] Prolactin levels and tumor size typically remain stable during nursing. In patients with a macroadenoma requiring treatment after delivery, dopamine agonists are administered, and therefore, nursing is not possible.

AREAS OF UNCERTAINTY

Although the majority of studies have been reassuring,[49] some studies have shown an increase in tricuspid regurgitation among patients treated with cabergoline.[33,34] Large prospective studies with long-term follow-up are needed to determine whether dopamine agonist therapy is associated with clinically significant cardiac-valve abnormalities in patients with prolactinomas. Longer-term prospective data are needed to guide decisions regarding the discontinuation of dopamine agonists and follow-up of these patients.

GUIDELINES

The Pituitary Society has published guidelines for the diagnosis and management of prolactinomas[50]; the recommendations in this article are generally concordant with the guidelines. These guidelines suggest that discontinuation of dopamine agonist therapy can be attempted in selected patients who have had normal prolactin levels for at least 2 years and minimal residual tumor volume. However, such patients need to be followed carefully, since tumor recurrence is common, particularly in the case of macroadenomas.

CONCLUSIONS AND RECOMMENDATIONS

The man described in the vignette has clinical manifestations of hyperprolactinemia and a macroprolactinoma. Pituitary function should be tested in patients with macroadenomas, and visual-field testing is mandatory when tumors are adjacent to the optic chiasm. Although microadenomas may or may not require therapy, macro-

adenomas do require therapy. Dopamine agonists are recommended for first-line therapy and typically decrease both prolactin levels and tumor mass, thereby relieving symptoms. On the basis of data suggesting that cabergoline has a better side effect profile and is more effective than bromocriptine, cabergoline is usually preferred, except in women seeking fertility; however, given limited data suggesting a possible association between cabergoline and cardiac-valve disease, bromocriptine may be preferred by some patients and physicians. If a normal prolactin level is maintained and if there is minimal residual tumor during medical therapy, available data suggest that it may be reasonable to discontinue therapy after 2 years, although recurrence rates are high and close follow-up is necessary.

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