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Prolactinoma Management

Mark E Molitch, MD
Division of Endocrinology, Metabolism and Molecular Medicine, Department of Medicine Northwestern University Feinberg School of Medicine, Chicago, IL 60611
Email: ude.nretsewhtron@hctilom
Juliana Drummond, MD
Department of Internal Medicine of the Federal University of Minas Gerais, Belo Horizonte/Minas Gerais, 30130-100, Brazil
Email: moc.liamtoh@etteduaebuj
Marta Korbonits, MD, PhD, DSc, FRCP
Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, UK
Email: ku.ca.lumq@stinobrok.m
Corresponding author.

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CLINICAL RECOGNITION

Patients with prolactinomas come to clinical recognition because of the effects of elevated prolactin levels or tumor mass effects. The most typical symptoms of hyperprolactinemia in premenopausal women are oligo/amenorrhea (approximately 90%) and galactorrhea (approximately 80%). Non-puerperal galactorrhea may occur in 5-10% of normally menstruating, normoprolactinemic women, and therefore is suggestive, but not definitive, of hyperprolactinemia. However, when oligo/amenorrhea is associated with galactorrhea, about 75% of women will be found to have hyperprolactinemia. Galactorrhea is reported in ~10% of cases in men with prolactinomas and is virtually pathognomonic of a prolactinoma. Hyperprolactinemia inhibits the pulsatile secretion of gonadotropin releasing hormone via interfering with hypothalamic kisspeptin-secreting cells via the

prolactin receptor, and may involve an opioid link.

Table 1.

Etiologies of Hyperprolactinemia

Pituitary Disease
Prolactinomas, Acromegaly, Empty Sella syndrome, Hypophysitis,
Hypothalamic Disease
Craniopharyngiomas, Meningiomas, Germinomas, Clinically non-functioning pituitary adenomas, Other tumors, Sarcoidosis, Langerhans cell histiocytosis, Neuraxis irradiation, Vascular, Pituitary Stalk Section
Medications
Phenothiazines, Butyrophenones, Atypical Antipsychotics, Tricyclic Antidepressants, Serotonin Reuptake Inhibitors, Reserpine, Methyldopa, Verapamil, Metoclopramide
Neurogenic
Chest wall/Breast lesions, Spinal Cord lesions
Other
Pregnancy, Breast-feeding, Hypothyroidism, Renal Insufficiency, Adrenal Insufficiency, Ectopic prolactin production, Familial hyperprolactinemia (mutated prolactin receptor), Untreated phenylketonuria
Idiopathic

PATHOPHYSIOLOGY

Prolactinomas comprise 25 to 40% of all pituitary adenomas. The vast majority of prolactinomas are sporadic. Familial cases of prolactinomas are very rare and occur usually in association with Multiple Endocrine Neoplasia type 1 or the Familial Isolated Pituitary Adenoma syndrome. Genetic testing for young-onset macroprolactinomas should include the *MEN1* and *AIP* genes. Similar to other types of pituitary adenomas, prolactinomas arise from a single transformed cell (lactotroph) with monoclonal proliferation. A number of candidate genetic alterations involved in the genesis and progression of prolactinomas have been looked for but no specific mutations have been found that account for more than a handful of cases at this point.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The majority of patients with hyperprolactinemia do not actually have prolactinomas (Table 1). Drug-induced hyperprolactinemia is the most common, and a number of physiological conditions, including stress (psychological or associated with acute illness), exercise, and sleep can also cause prolactin elevations. The hyperprolactinemia caused by drugs and other non-prolactinoma causes is usually <150 ng/mL (3000 mU/L). Many medications block dopamine release or action, the most common being antipsychotic medications, verapamil and metoclopramide. The best way to determine whether hyperprolactinemia is drug-induced or not is to discontinue the drug or switch to another drug in a similar class that is not known to cause hyperprolactinemia and see if the prolactin levels return to normal within 72 hours. The best example is the partial dopamine receptor agonist aripiprazole, which has been shown to be effective in attenuating antipsychotic medication-induced hyperprolactinemia.

A variety of suprasellar lesions cause hyperprolactinemia because compression of the hypothalamus or pituitary stalk results in decreased dopamine reaching the lactotrophs. These can be mass lesions, such as craniopharyngiomas or meningiomas, or infiltrative disease, such as sarcoidosis and Langerhans cell histiocytosis. The high estrogen levels of pregnancy cause lactotroph hyperplasia and hyperprolactinemia, so pregnancy must always be excluded. The estrogen levels produced by oral contraceptives or post-menopausal hormonal replacement therapy generally do not cause hyperprolactinemia. Hypothyroidism and renal failure (serum creatinine >2 mg/dL (176 µmol/L)) can also cause hyperprolactinemia. Thus, the initial laboratory evaluation involves repeat measurement of prolactin, measurement of TSH and serum creatinine, and a pregnancy test. Unless there is very good evidence for these conditions or drug-induced hyperprolactinemia, even patients with mild hyperprolactinemia should be evaluated with radiological methods, preferably MRI, to distinguish among idiopathic hyperprolactinemia, microprolactinomas, and large mass lesions. Measurement of IGF-1 is recommended for patients presenting with hyperprolactinemia and pituitary adenomas as prolactin may be elevated in up to 50% of patients with GH-secreting tumors.

Special caution is needed when two-site ('sandwich') prolactin assays are used, as patients with large prolactinomas and very high prolactin levels may appear to have prolactin levels that are normal or only modestly elevated, thus mimicking a large, non-functioning adenoma. This "hook effect" is due to saturation of the assay antibodies and prolactin levels should always be remeasured at 1:100 dilution in patients with large macroadenomas and normal to modestly elevated prolactin levels.

Sometimes prolactin levels are elevated due to increased amounts of macroprolactin. Macroprolactin consists of high molecular weight prolactin variants that are either aggregates with immunoglobulins or dimers, and have diminished biologic potency. Macroprolactin can be detected in the serum by precipitating the complex with polyethylene glycol. In normal individuals, macroprolactin comprises < 30% of circulating prolactin; therefore, if after precipitation with polyethylene glycol the prolactin levels in the supernatant are > 70% of the upper limit of normal for the assay, the patient can be assumed to have true hyperprolactinemia and not an elevation due simply to macroprolactin.

Macroprolactinemia has usually been found in patients with equivocal symptoms and not those typically due to hyperprolactinemia. A lack of recognition of the presence of macroprolactin can lead to unnecessary laboratory investigations, imaging, and pharmacologic or surgical treatment.

When no pituitary lesions are seen by radiological studies and other known causes have been excluded, the diagnosis of idiopathic hyperprolactinemia is made; in long term follow-up, although prolactin levels may rise to over 50% of the baseline in 10-15% of the patients, only about 10% develop detectable microadenomas, one-third resolve their hyperprolactinemia without specific intervention, and prolactin levels remain stable in most patients.

TREATMENT

Figure 1. . Serum prolactin measurement is required in all patients presenting with hypothalamic-pituitary lesions before surgery is accomplished (Figure courtesy of D.

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Not all patients require treatment. If a patient with a microadenoma or idiopathic hyperprolactinemia presents with non-bothersome galactorrhea and has normal estrogen/testosterone levels they can simply be followed with periodic prolactin levels. Similar patients who may have amenorrhea but are not interested in fertility may be treated with estrogen replacement. However, for most symptomatic patients, a dopamine agonist is the therapy of choice. Dopamine agonists normalize prolactin levels, correct amenorrhea-galactorrhea, and decrease tumor size by more than 50% in 80-90% of patients, with cabergoline generally being more efficacious and better tolerated than bromocriptine. Thus, defining whether a pituitary tumor is a prolactinoma is crucial for optimal patient management since it is reasonable to use cabergoline as first-line therapy even in patients with visual field defects as long as visual acuity is not threatened by rapid progression or recent tumor hemorrhage (Figure 1). Starting dose in these cases could be higher than usual and some experts suggest 0.5 mg/day with close in-patient monitoring.

Vision often starts to improve within days after the initiation of dopamine agonist therapy. Cabergoline is usually initiated at 0.25-0.5 mg/week (taken initially carefully a with meal just before bedtime, to reduce nausea and improve compliance), whereas the initial dose of bromocriptine is 1.25 mg/day. About 40-50% of patients, whose prolactin levels normalize and tumors shrink to the point of non-visualization, can be tapered off cabergoline without tumor re-expansion. Factors associated with greater risk of recurrence are the presence of pituitary deficits at diagnosis and higher prolactin levels, both at diagnosis and before withdrawal.

A rare but significant side-effect of dopamine agonist treatment is cerebrospinal fluid leakage (CSF) leak, due to the rapid shrinkage of a large prolactinoma allowing CSF to escape if significant damage is present at the fossa floor. Patients should be advised to present if clear fluid appears and this should be tested for beta-2 transferrin. If positive, patients need urgent neurosurgical input with transnasal surgery or lumbar drain being possible approaches in addition to antibiotic therapy, if necessary. Discontinuing dopamine agonist therapy is not usually recommended as it may cause recurrence of the tumor. Dopamine agonist therapy has been implicated as a precipitating factor for pituitary apoplexy in patients with prolactinomas. Nonetheless, prolactinomas are, by themselves, more prone to bleeding, and the reported prevalence of pituitary apoplexy in macroprolactinomas treated with dopamine agonists, ranging from 1% to 6%, is not significantly different from the rate recorded in untreated prolactinomas. Further precipitating factors which have been associated with pituitary apoplexy are cerebral angiography, surgical procedures, head trauma, dynamic tests, anticoagulation therapy, and pregnancy.

A well-described side-effects of dopamine agonists include psychiatric complications, such as depression, anxiety, insomnia, hallucinations, mania. More recently impulse control disorders have also been described in pituitary adenoma patients. The underlying mechanism is related to an interaction between the dopamine agonists and the D3 receptor in the mesolymbic system. Impulse control disorders can manifest as hypersexualism, gambling, compulsive eating, compulsive shopping, and "punding" (compulsive performance of and fascination with repetitive mechanical tasks, for example assembling and disassembling household objects or collecting or sorting various items), with hypersexualism and gambling being the most commonly observed in pituitary patients. Hypersexualism has also been described in teenage children. Although impulse control disorders are infrequent, they have the potential to cause devastating consequences on patients' life and clinicians should be sensitive to these potential side-effects discussing it with the patient at the start of treatment and during long-term follow-up. Discontinuation of the dopamine agonists usually reverses these side-effects.

In some cases, prolactinomas appear to be resistant to a dopamine agonist, but it is important to ensure compliance and to be certain that the underlying lesion is a prolactinoma and not some other cause of hyperprolactinemia. About 50% of patients resistant to bromocriptine will respond to cabergoline. Most patients resistant to standard doses of cabergoline respond to larger doses. Previous reports in patients taking cabergoline for Parkinson's disease have shown that doses >3 mg/day may be associated with cardiac valvular abnormalities. Whether similar valvular changes occur in patients receiving low-dose cabergoline for treatment of hyperprolactinemia is still debatable. Common practice has been to perform periodic echocardiograms every 12 to 24 months in patients taking >2 mg/week. However, a clinically significant association between low-dose cabergoline and cardiac valvulopathy is not supported by a large recent multicenter follow-up study. More recently, a meta-analysis of case-control studies evaluating patients who had received ≥6 months cabergoline treatment for hyperprolactinemia reported an increased risk of tricuspid regurgitation in the cabergoline-treated patients compared to controls. Nevertheless, these results were mainly influenced by the results from a single center and in the majority of the reviewed studies there were no cases of moderate-severe tricuspid regurgitation in either group. Furthermore, neither cumulative dose nor treatment duration was associated with an increased risk of moderate-severe valve lesions and none of these lesions were found as a result of cardiac symptoms. Therefore, these data would suggest that some degree of monitoring is appropriate, although at substantially reduced frequency than currently recommended. Indeed, some experts suggest echocardiographic monitoring should be reserved for those patients with an audible murmur, those treated for more than 5 years at a dose of more than 3 mg per week, or those who maintain cabergoline treatment after the age of 50 years.

An alternative approach is transsphenoidal surgery, which has initial remission rates of approximately 75% for microprolactinomas and 40% for macroadenomas, and long-term recurrence rates of nearly 20% and 35%, respectively, when performed by expert neurosurgeons. Transsphenoidal surgery is usually reserved for patients with resistance or intolerance to dopamine agonists; macroprolactinomas with chiasmal compression and visual deficits without rapid improvement on medical treatment; or with acute tumor complications, such as symptomatic apoplexy or cerebrospinal fluid leakage. Complications of hypopituitarism, infections and bleeding are minimal, but increase proportionately with tumor size. Craniotomy for large tumors is rarely curative and is fraught with much higher complication rates. Radiation therapy is reserved for those patients with macroadenomas not responding to either medical or surgical treatment. Radiation therapy in all forms is associated with a high rate of hypopituitarism that develops gradually over many years. Temozolomide, an orally-active alkylating chemotherapeutic agent, is reserved for the treatment of aggressive prolactinomas refractory to other treatment modalities.

FOLLOW-UP

The goals of treatment are to normalize prolactin levels or at least bring them to levels at which gonadal/reproductive/sexual function is normalized and to decrease tumor size. As noted, according to different series, nearly 80% of patients treated with dopamine agonists will reach these prolactin goals and achieve significant tumor size reduction. Once prolactin levels have reached normal or near-normal level, they can just be monitored every 3-6 months for the first year and then every 6-12 months thereafter. Macroadenoma tumor size can be monitored by serial MRI scans and once maximal size reduction has been documented, further scans may not be necessary as long as prolactin levels are being monitored. Whether a second MRI scan is necessary in patient with microadenomas is debatable, if prolactin levels are regularly monitored. It is extremely rare for a tumor to increase in size without there being a significant increase in prolactin levels. Visual field testing should be repeated until they normalize or remain stable and then do not need to be repeated.

PREGNANCY

Dopamine agonists have to be given to allow ovulation to occur and then are usually stopped once pregnancy is diagnosed. In this fashion, the developing fetus has been exposed to the drug for about 4-6 weeks. There do not appear to be any risks for fetal malformations or other adverse pregnancy outcomes with either bromocriptine or cabergoline. Data on exposure of the fetus to cabergoline during the first few weeks of pregnancy have now been reported in more than 900 cases and suggest that cabergoline is as safe as bromocriptine in this context. Dopamine agonists are then reinstituted when breast-feeding is completed. Symptomatic growth occurs in about 23% of macroprolactinomas and about 3% of microprolactinomas in the second or third trimester due both to the stimulatory effect of the high estrogen levels of pregnancy and the withdrawal of the dopamine agonist that may have been restraining tumor growth. Visual field testing should be carried out each trimester in patients with macroadenomas but in those with microadenomas only when they develop visual symptoms or progressive headaches. MRI scans (without gadolinium) are done in those patients who develop visual field defects or severe headaches when a therapeutic intervention is contemplated. Prolactin levels may rise during pregnancy when there is not a change in tumor size and conversely, some tumors enlarge without an associated rise in prolactin; therefore, measurement of prolactin during pregnancy need not be carried out. When there is evidence of significant symptoms and tumor growth, the patient should be restarted on a dopamine agonist. Again, there are fewer data with cabergoline than bromocriptine but there is no particular reason to favor one versus the other in this context. Transsphenoidal surgical decompression can be performed if there is an unsatisfactory response to the dopamine agonist. Delivery of the baby and placenta can also be initiated if the pregnancy is sufficiently advanced.

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