Hyperprolactinemia and prolactinoma: selected issues.

Dana Erickson MD, Associate Professor of Medicine
Mayo College of Medicine, Rochester MN.

Objective:
In my presentation, I will discuss selected issues in management of patients with hyperprolactinemia and prolactinomas and illustrate the following points in various cases seen at our clinic.

1. Diagnostic pitfalls: macroprolactin
2. Therapeutic issues
   a. Length of therapy with dopamine agonist
   b. Cardiac concerns in patients treated with dopamine agonist
   c. Obsessive compulsive disorders in patients on dopamine agonist therapy
   d. Hemorrhage in prolactinomas
   e. Effects of pregnancy on prolactinoma
   f. Effects of dopamine agonist therapy on offspring
   g. Effects of lactation on course of prolactinomas
   h. Gamma knife therapy in prolactinomas

Introduction:
Prolactinomas are pituitary adenomas that express and secrete prolactin. They are found in about 5% of autopsy studies of pituitaries and account for 30 to 40% of clinically recognized pituitary tumors. Ninety percent of prolactinomas are microadenomas; the rest represent macroadenomas. Clinical features include oligomenorrhea up to 90% of women and galactorrhea up to 80%. Infertility, hirsutism, and acne can be present as well. Men present with reduced libido, impotence, infertility, gynecomastia, rarely galactorrhea. While typical microprolactinoma associated with normal pituitary function, a macroprolactinoma can be associated with symptoms of mass effect such as headache, bitemporal hemianopsia, cranial nerve palsies or various degrees of hypopituitarism. The diagnosis requires both radiographic evidence of pituitary adenoma and laboratory analysis documenting the presence of hyperprolactinemia. In general, serum prolactin levels parallel the size of the tumor. In most patients with prolactin over 150 mcg/dL will harbor a prolactinoma. Not every lesion seen on MRI pituitary represents prolactinoma and stalk effect (enlarged nonfunctioning pituitary masses or various etiology shifting the pituitary stalk should be taken into consideration). Most patients with symptoms from prolactinoma will require additional treatment, although data suggests that if microprolactinomas are not treated, tumor expansion is seen in only 7% of patients. Primary goal in patients with microprolactinoma is to restore gonadal sexual function while in macroadenomas reduction and control of the tumor size is of importance. Patients with microprolactinomas who choose not
to have therapy intervention, such as women with regular menstrual cycles and tolerable galactorrhea or post-menopausal women without significant galactorrhea or men without significant hypogonadism should be periodically monitored.

Pharmacotherapy includes, in the United States, bromocriptine and cabergoline. These medications typically lower serum prolactin level and induce tumor shrinkage. Medications differ by affinity for D2 receptor and their half-life. Reported studies show prolactin normalization varied between 52% and 82% of patients on bromocriptine and 80 to 85% of patients for cabergoline. Normalization and gonadal function has been seen in 70 to 85% of patients treated with bromocriptine and 82 to 93% of patients treated with cabergoline. Tumor sizes decreased by using dopamine agonists in setting of microprolactinoma quite frequently, and in setting of macroprolactinoma if responsive tumor bromocriptine reduces more than 50% the size of the tumor in 40 to 55% of cases and cabergoline decreases tumor size between 30 and 50% in more than 90% tumors after length of treatment at least 24 months. Visual fields improve in 90% of patients when on medical therapy.

1. Diagnostic pitfalls: macroprolactin.
Idiopathic hyperprolactinemia has been reported in 20 to 30% of patients with prolactin elevations. This diagnosis is reached after exclusion of secondary causes of hyperprolactinemia such as pregnancy, renal liver disease, and primary hypothyroidism as well as in the absence of medications known to induce prolactin elevations, chronic nipple stimulations. Typically this description is used in a setting of negative MRI.

It has been recognized that human prolactin exists in multiple molecule forms as monomeric, big prolactin and big-big prolactin (macroprolactin). Macroprolactin is a complex of monomeric prolactin with IGG antibody and can be frequently detected by prolactin immunoassays and various assays have different cross reactivity with the macroprolactin. This macroprolactin generally is not biologically active. Presence of macroprolactin is confirmed by polyethylene and glycol precipitation in which macroprolactin is removed from the serum. Typically recovery of prolactin more than 50% after precipitation with specific indicated that macroprolactin is not present in significant amounts; however, if the recovery is less than 50%, there is consistently high macroprolactin. Studies comparing various assays for prolactin showed significant variations between methods and macroprolactinemia issues.

Reporting of presence of degree of macroprolactinoma is rather complicated for clinician interpretation. Our laboratory has been developing methods to look at post peg precipitation normal reference interval which would be gender specified using Roche immunoassay. This might become quite useful for clinicians for analysis of presence of macroprolactin in the future. We would consider checking for presence of macroprolactinemia prior to labeling the patient with idiopathic hyperprolactinemia. Although macroprolactin has now been recognized as a common cause of
hyperprolactinemia, especially in certain assays, commercial and laboratories do not routinely screen for this form of prolactin, and therefore, clinicians have to be aware of the possibility of screening for this entity.

2. Therapeutic issues.
A. Dopamine agonist discontinuation. Major study published in 2003 and follow-up in 2007 by Colao et al. revealed that out of 221 patients treated (115 microprolactinomas, 79 macroprolactinomas, 27 idiopathic hyperprolactinemia) who were initially treated for 2 years with cabergoline and met strict criteria for withdrawal of dopamine agonist, 47% of microprolactinoma, 57% patients with idiopathic hyperprolactinemia, and 44% of patients with macroprolactinoma maintained normoprolactinemia after 24 to 96 months follow up. Analysis in the later study via multiple regression showed that nadir prolactin levels and nadir maximal tumor diameter prior to withdrawal was a statistically significant predictor of remission as was a maximal tumor diameter at the initial diagnosis. Recently published metaanalysis (2011) reviewed persistent normoprolactinemia after dopamine agonist withdrawal in 19 studies. Persistent normoprolactinemia was present in 21% patients using random effect model (35% in patients initially treated with cabergoline as compared to 19% in patients treated with other agents). When the metaanalysis was broken into the causes of hyperprolactinemia, idiopathic hyperprolactinemia had the most persistent remission in 32% of cases versus microprolactinoma in 21% and macroprolactinoma in 16% of patients. The treatment duration appears to have an effect as well. If the treatment with dopamine agonists was less than 25 months, the random effect model for persistent normal prolactinemia was 16% versus 25% in patients treated more than 25 months. However, since the metaanalysis, there were two additional studies which showed relatively higher risk of recurrence in patients with macroprolactinomas. As per Endocrine Society guidelines from 2011, dopamine agonist therapy might be tapered and perhaps discontinued in patients with normal serum prolactin for at least two years and minimal remnant of MRI visible tumor. Patients will need a long-term followup.

B. Cardiac concerns in patients treated with dopamine agonist? In 2007, there were two major studies published in Medical Journals in regards of patients of patients treated with pergolide or cabergoline for Parkinson’s disease. They found an increase prevalence of cardiac valvular disease in patient treated with cabergoline and pergolide, not bromocriptine. There appear to be a clinically important regurgitation of moderate to severe degree in any cardiac valve in patients taking cabergoline (28.6%) as well as pergolide (23%), but not in patients taking nonergot-derived dopamine agonists as bromocriptine (0%). The relative of risk of moderate to severe valve regurgitation for cabergoline was 4.6 for mild regurgitation 7.34 aortic valve regurgitation and 5.5 for tricuspid valve regurgitation. There was also an increase in the tenting area of the cardiac valves. The risk was particularly
Increased with a dose of cabergoline of more than 3 mg per day. The pathophysiological explanation behind these findings might be activation of 5-hydroxy-tryptophan receptors expressed on heart valves. Cabergoline and pergolide are both agonists of the receptor whether the other agents such as bromocriptine have antagonistic properties. Preferential activation of these receptors has been shown to induce prolonged microgenic in cardiac fibroblasts which could include valvular hyperplasia. In general, this has sparked a significant amount of studies in the endocrine field, with analysis of information available for patients treated with dopamine agonists. Between the years of 2008 and 2013, about ten studies were published in this field and the majority of the studies did not reveal a significant increase in moderate to severe valvulopathy in patients on cabergoline for indication of prolactinoma versus controls. Exception appears to be study from Colao et al. in 50 patients where authors found an increased risk of moderate tricuspid regurgitation (54% versus 18% in controls). Majority but not all of the studies also do not show an increased risk of mild tricuspid valve regurgitation versus controls, although the mild tricuspid regurgitation is not thought to be clinically relevant. As example study by Halperin et al. in 2012, revealed having slightly higher prevalence of mild tricuspid regurgitations in patients with higher dosages. The median durations in these studies of treatment was anywhere between 46 to 79 months, and the cumulative dosages of reported studies varied between 173 mg of to 7000 mg of cabergoline. Cross-sectional study by Wakil et al. in 2008, reported more prevalence of aortic valve calcifications in patients on cabergoline. Most recent report from U.K. from a large cross-sectional study of 747 patients (vast majority on cabergoline with a median cumulative dose of 152 mg) showed a low 3.2% prevalence of moderate cardiac valvular disease, and there was no association between cumulative dose and side effects. It is an important point to point out that there are studies showing that the blinding of the echocardiographer is of most importance in interpretation of the findings. One longitudinal study by Delgado et al. published in 2013 of 74 patient (follow up of Wakil data), of whom 45 were on cabergoline, showed longitudinally increase rate of calcifications from 39 to 53% in cabergoline group, however, no increase in valvular dysfunction. Putting this data together, it does not appear that there is a definitive increased risk of clinically significant cardiac valve disease at this point; however, patients who are on very high dosages of cabergoline long term might have a reasonable indication to periodically perform echo.

C. Impulse control disorders?
There are several reports in literature of impulse control disorders on dopamine agonist therapy in patients with Parkinson's disease and few anecdotal reports in patients taking dopamine agonists for prolactin producing tumors. Recently we have looked at a group of 77 patients treated for prolactin producing tumors and compared with 70 patients with nonfunctioning tumors via approved questionnaires for impulse control disorders. The groups were quite matched for size of the tumor, age, sex, psychiatric disorders, and other underlying pituitary diseases, and we found an increased risk of hypersexuality in
patients with prolactinomas treated with dopamine agonists of 12% versus nonfunctioning tumors 2.8%. Statistically, this was in particularly seen in men. Other obsessive-compulsive disorders such as excessive gambling, excessive shopping and puniting were not more prevalent in treated prolactinomas than nonfunctioning tumors; however, in general, the prevalence was higher in both groups (24.5% and 17%) than in reported healthy population.

D. Hemorrhage and apoplexy in prolactinomas.
Patients often ask about risk of bleeding in their tumors. Two more recent studies address some of these issues. Chang reported a case of apoplexy (defined as sudden severe headache, cranial nerve palsy, nausea, impaired pituitary function) and reviewed literature in patients on cabergoline (n=13) reported in the literature (the condition appears to be extremely rare). Headaches (61%) and visual impairment (31%) were the most common presenting features followed by cranial nerve palsies (23%) and altered mental status (15%). Majority of patients had macroadenomas with underlying cystic degeneration. Ten of them required surgical management, 3 were treated conservatively. Surgery was performed within 7 days of acute presentation and 5/10 patients were continued on dopamine agonist therapy. In majority of patients the hormonal abnormalities which developed after apoplexy persisted on further follow-up. Interestingly, asymptomatic hemorrhage was found in 25/368 patients (6.8%) of a recent prevalence study of prolactinomas. Three of these presented as apoplexy, the rest was mostly seen on imaging at the initial diagnosis (72%). The findings of hemorrhage were seen predominantly in women with large tumors. Hemorrhage resolved in 90% of cases at average of 26 months. Minority of these patients developed hypopituitarism.

E, F, G Prolactinomas and pregnancy.
Appropriately treated prolactin producing tumors lead to normalization of fertility in women, and in general, the recommendation is to discontinue dopamine agonist therapy at the time of confirmation of pregnancy. There is data (reviewed by Dr. Molitch in Best Practice and Research Endocrinology in 2011) on 6239 women who conceived on bromocriptine and 789 women who conceived on cabergoline with subsequent discontinuation of these medications and it did not show an increase incidence of spontaneous abortions, ectopic pregnancies, or hydatiform moles. There is no increased risk of preterm delivery and no significant increased risk of multiple births. Babies did not have increased risk of congenital malformations (bromocriptine 1.8%, cabergoline 3.2% versus normal 3%). As far as enlargement of prolactinomas, there appears to be a small risk of enlargement in patients with microprolactinomas (2.7% from 658 patients), significantly increased risk in patients with a macroadenoma with no prior surgical or radiation therapy (22%), and in 4.8% of patients with prolactinomas who had prior surgical therapy. Therefore, patients whose treatment with dopamine agonists is discontinued at
the time of pregnancy confirmation should have a periodic assessment throughout pregnancy perhaps on a trimester basis for any visual problems and headaches. Prolactin levels in general are not followed during pregnancy as pregnancy, per se, increases prolactin levels. Study by Lebe et al. followed patients throughout the pregnancy and in fact, did routine imaging in 17 out of 37 cases at 24 to 32 weeks of gestation and found an increase in tumor size of 2 to 8 mm. Cabergoline needed to be restarted in 5 of these patients due to visual field problems and headaches. Spontaneous remissions of hyperprolactinemia after pregnancies have been reported, and studies report remission rate between 17 - 35% after completion of pregnancy. A recent study by Auriemma et al. in 2013 reported lack of hyperprolactinemia in 68% of patients followed up to 60 months after delivery. Breast feeding either less than two months or two to six months did not appear to increase risk of recurrence of the tumor or the degree of prolactin elevation after cessation of breastfeeding. The group of patients in this study, who underwent the repeated MRI of head three to six months after pregnancy, did not show any tumor enlargement.

H. Gamma-knife therapy.

Patients who are intolerant to dopamine agonist therapy and need active treatment or whose tumors grow despite adequate dopamine agonist therapy would have a consideration of transsphenoidal endoscopic or microscopic surgical removal of tumor. The surgical cure rates for microprolactinomas are in general between 75% and 80% with a recurrence of hyperprolactinemia after initial normalization in 15 to 20% of patients. In macroprolactinomas it is less likely to achieve successful remission after surgery and long-term surgical cure in is 25%. Radiotherapy is not generally considered a secondary treatment in prolactinomas, however, has been used in patients who are deemed not to be good candidates for surgery or perhaps in patients, (as the patient number 4), who are intolerant to medication therapy and has location of the prolactinoma in cavernous sinus. The treatment is relatively well tolerated. However, the reported rate of remission is relatively low, between 18 and 37% of normalization of prolactin after median followup, between 29 to 60 months. The number of patients reported receiving this treatment is still relatively low, less than 300 patients. Our group results shows a remission in about 18% of patients at a median of 34 months; however, an additional 32% of patients had improved symptoms, or it was possible for them to discontinue medications with a mildly normal elevated prolactin. Another 14% had improvement of control in symptoms on a lower dose of medications. However, at the median followup of 19 months, 38% of patients developed a new partial pituitary insufficiency. In general, gamma knife therapy would be the last possible option for a patient intolerant to medications with symptoms due to hyperprolactinemia such as galactorrhea and a location of the tumor which is not accessible to surgery.

Selected References


No clinically significant valvular regurgitation in long-term cabergoline treatment for prolactinoma. *Clinical Endocrinology*. 2012;77, 275-280