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Evaluation and management of hyperprolactinemia

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Hyperprolactinemia is encountered fairly commonly in a referral practice of general or reproductive endocrinology. The clinical manifestations of this biochemical perturbation are limited in number, usually insidious in onset, and non-emergent in nature, so the diagnosis is often delayed for months or years after symptoms first appear. Fortunately, once an elevation in the serum prolactin level is confirmed, the subsequent diagnostic evaluation to establish the underlying cause is generally uncomplicated, and successful treatment is almost always possible.

Clinical presentation: In most laboratories, the upper limit of normal for prolactin is around 20 ng/mL ($\mu\text{g/L}$). The predominant physiologic consequence of hyperprolactinemia is hypogonadotropic hypogonadism, which is due to suppression of gonadotropin releasing hormone (GnRH). The clinical manifestations of conditions associated with hyperprolactinemia vary significantly depending on the age and sex of the patient and the magnitude of the prolactin excess.

Premenopausal women: May present with infertility, oligo/amenorrhea, or galactorrhea. Mild elevations of prolactin (20 - 50 ng/mL) may cause only insufficient secretion of progesterone, resulting in a short luteal phase and decreased fertility but no disturbance of the menstrual cycle. Higher levels (50 - 100 ng/mL) are usually associated with menstrual dysfunction, while levels above 100 ng/mL are frequently associated with overt hypogonadism and its usual sequelae, including vasomotor symptoms, vaginal dryness with dyspareunia, decreased libido, and decreased bone mass. It is worth noting that many premenopausal women with hyperprolactinemia do NOT have galactorrhea, and many patients with galact-

orrhea do NOT have hyperprolactinemia, particularly in the absence of associated menstrual dysfunction.

Postmenopausal women: Since postmenopausal women who do not take estrogen replacement are clearly hypogonadal, and estrogen priming of the breast is necessary for milk production, galactorrhea is very uncommon. Hyperprolactinemia in this group of patients is generally recognized only after an intra- or parasellar mass is suspected because of headaches or visual aberrations.

Men: The hypogonadism associated with hyperprolactinemia may result in erectile dysfunction, decreased libido, infertility, gynecomastia, decreased bone mass, and (rarely) galactorrhea. As would be expected, there is a general correlation between the magnitude of the prolactin elevation and the number and severity of these symptoms. Over time, the patient may notice diminished energy as well as decreased muscle mass and strength.

CAUSES OF HYPERPROLACTINEMIA

Physiologic causes: The most common cause of hyperprolactinemia is the hyperestrogenemia of pregnancy. Prolactin levels start to rise within several weeks of conception and reach peak values of up to 600 ng/mL by delivery. Post-partum nipple stimulation with suckling results in progressively diminishing degrees of prolactin elevation over time, as the hyperestrogenemia of pregnancy dissipates. Nipple stimulation in non-lactating women causes little if any rise in prolactin. Physical or psychological stress can also be associated with an elevation in prolactin, but the magnitude is much less impressive, with levels rarely rising above 40 ng/mL. In rare

patients, elevated serum levels can be attributed to delayed clearance of prolactin caused by aggregation of the molecules because of excessive glycosylation ("big prolactin") or circulating prolactin antibodies. The former can be distinguished by gel filtration or precipitation using polyethylene glycol, while the latter can be clarified by a normal free prolactin concentration. Neither of these last two conditions is associated with any pathologic consequences, so they would only be serendipitously discovered in clinical practice.

Pathologic causes: Prolactin levels can become pathologically elevated through a variety of different mechanisms. These etiologies can be conveniently subdivided as follows:

Medications: Usually cause prolactin elevation by blocking the normally dominant inhibitory receptors for dopamine on the pituitary lactotroph cells (metoclopramide, domperidone, risperidone, sulpiride, haloperidol, phenothiazines, tricyclic antidepressants, cimetidine) or directly interfering with the synthesis or storage of dopamine (methyl dopa, reserpine, monoamine oxidase inhibitors). Estrogens amplify the normal pituitary secretion of prolactin. Verapamil (but not other calcium channel blockers) has been shown to raise prolactin levels, although the mechanism is unknown. Other agents that have been reported to cause hyperprolactinemia include cocaine, fluoxetine, and protease inhibitors.

Lactotroph adenomas: Are by far the most common secretory pituitary tumors. Most secrete only prolactin, but about 10% also contain somatotroph cells and also secrete growth hormone. They are most commonly diagnosed in premenopausal women, presumptively because the associated menstrual dysfunction brings them to medical attention. Tumors found in men are usually larger, which is likely due to delayed diagnosis related to the nonspecific nature of the associated symptoms. There is a rough correlation between the size of the tumor and the magnitude of the associated prolactin elevation, with macroadenomas of 1 - 2 cm diameter typically associated with prolactin levels of 200 - 1,000 ng/mL, and larger tumors with values > 1,000 ng/mL. Prolactin levels reported to be less than 200 ng/mL associated with a macroadenoma can often be seen with a non-lactotroph tumor, but might also be artifactually low with a lactotroph macroadenoma secondary to a "hook phenomenon", in which extremely high prolactin levels saturate both of the antibodies (capture and signal) used in the conventional "sandwich" chemiluminescent and immunoradiometric assays and inhibit their binding. In such a case, the prolactin assay should be repeated on a specimen that has been diluted 1:100.

Hypothalamic and pituitary diseases: Can interfere with the secretion of dopamine by the hypothalamus or

its delivery to the pituitary. Larger non-lactotroph pituitary tumors as well as a variety of benign (e.g., craniopharyngioma, Rathke's cleft cyst) and malignant (e.g., metastatic lung or breast cancer) non-pituitary tumors have been reported to cause hyperprolactinemia. Traumatic sectioning of the pituitary stalk and infiltrative diseases such as sarcoidosis are less common etiologies.

Severe hypothyroidism: Can result in prolactin elevation due to increased hypothalamic synthesis of and pituitary responsiveness to TRH. It should be emphasized that the thyrotroph (and lactotroph) hyperplasia associated with this condition may cause significant generalized enlargement of the pituitary gland, which can be radiologically confused with a lactotroph adenoma.

Chest wall injuries and burns: May result in mild prolactin elevation due to neural stimulation (similar to suckling).

Chronic renal failure: Is associated with both increased prolactin secretion and decreased prolactin clearance.

Cirrhosis: Is also associated with mild elevations in basal prolactin levels in up to 20% of patients.

Idiopathic hyperprolactinemia: Is ultimately diagnosed in a significant percentage of patients with prolactin levels < 100 ng/mL. Some of these patients may simply have tiny lactotroph tumors that are just too small to be detected by current imaging techniques. From a clinical standpoint, most of these patients demonstrate stable levels over many years, with only a small percentage progressing to develop a detectable pituitary tumor, and up to 30% actually experiencing spontaneous normalization of their prolactin levels over time.

DIAGNOSTIC EVALUATION

A serum prolactin level should be measured in patients with the above symptoms. If hyperprolactinemia is biochemically confirmed, the cause must next be elucidated, so that appropriate therapy can be instituted. From a clinical standpoint, the initial focus should be on identifying a plausible non-tumorous etiology, which could then be successfully addressed without incurring the significant expense and inconvenience of CT and/or MRI scans. In the absence of such a pleasant discovery, it becomes absolutely necessary to perform radiologic imaging studies of the hypothalamic-pituitary region, since a large mass lesion in this anatomic location, even if benign, can ultimately result in permanent visual impairment and deficiencies of some or all other pituitary hormones.

A thorough clinician should inquire about the possibility of pregnancy and search for symptoms of hypothyroidism. A comprehensive review of all current and recent medications, including oral contraceptives, is a critical part of the evaluation. Headaches or visual aberrations should

alert one to the possibility of an intracranial mass. Up to 20% of patients with MEN1 will develop prolactinomas, which tend to be more aggressive than sporadic tumors, so a careful family history is essential. Physical examination should focus on detecting the presence of temporal visual field loss, goiter or signs of hypothyroidism, significant chest wall irritation, testicular size and texture, and body hair growth.

All patients with confirmed hyperprolactinemia of unclear etiology should have biochemical testing for pregnancy, hypothyroidism, and significant renal or liver disease. If these are non-revealing, an MRI of the head with selective pituitary cuts should be performed. If an intra or parasellar mass is discovered, further testing of other pituitary and end organ hormones is warranted, keeping in mind the possibility that the lesion could represent a pituitary "incidentaloma". If no lesion is seen, the workup is concluded with the diagnosis of idiopathic hyperprolactinemia.

TREATMENT OF HYPERPROLACTINEMIA

The mere existence of hyperprolactinemia does not automatically require treatment, and patients with mild stable prolactin elevation, small tumors, and minimal subjective discomfort may be safely observed for years. However, since most patients found to have an elevated prolactin level were initially evaluated because of symptoms that were ultimately attributable to this biochemical abnormality or to a tumor causing it, the majority of patients are deserving of therapy. Certainly, a therapeutic trial of a dopamine agonist would seem warranted in any patient in whom the relationship of their symptoms to this finding is unclear, and improvement in the patient's subsequent quality of life would favor continuation of this therapy.

TREATMENT OF NON-TUMOURS HYPERPROLACTINEMIA

If hyperprolactinemia is felt to be caused by a particular medication, the simplest solution is to discontinue the offending drug whenever possible, substituting with a different agent (if necessary) that is not prone to cause this problem. However, there are occasions in which the causative agent is judged to be essential for the patient's health (for example, a particular psychotropic agent that has been uniquely beneficial), yet the prolactin elevation is causing symptomatic hypogonadism. In such a patient, pharmacologic treatment with a dopamine agonist should be avoided, since it might compromise the effectiveness of the psychotropic drug, and the patient should simply be treated with replacement of sex steroids.

Patients with prolactin elevation due to severe hypothyroidism require no specific therapy with dopamine agonists, since optimal replacement therapy with exogenous levothyroxine will usually normalize the prolactin levels within several weeks. Patients with symptomatic prolactin elevation due to pituitary or hypothalamic disease that is not amenable to curative treatment should be treated with a dopamine agonist.

TREATMENT OF LACTOTROPH ADENOMAS

Dopamine agonist drugs have been in clinical use for over 25 years, and have become the principal therapeutic choice for prolactin-secreting pituitary tumors. These agents decrease prolactin levels significantly in the vast majority of patients, and are usually effective in diminishing the size of the tumor as well. All (except quinagolide) are ergot derivatives and have been associated with nausea, vomiting, postural hypotension, mental fuzziness, digital vasospasm, nasal stuffiness, constipation, and depression. These symptoms are most likely to occur with initiation of treatment or when the dose is increased. Patients who are intolerant or fail to respond to one agent may do well on another.

Bromocryptine: Has been in use since the late 1970's. Its short half-life requires twice daily administration to maintain optimal suppression of prolactin levels. It is the agent most likely to cause the above side effects. If gastrointestinal side effects limit use, the 2.5 mg tablets can be administered intravaginally once daily with much better tolerance. A dose of 2.5 mg bid costs \$137.00 for a one-month course of therapy in my local pharmacy.

Cabergoline (Dostinex): Is the most potent and best tolerated of these drugs, with a very long half-life allowing twice-weekly dosing in most patients. It can also be given intravaginally if nausea occurs when taken orally. Unfortunately, it is extremely expensive, costing \$300.00 for a typical one-month supply of eight 0.05 mg tablets.

Pergolide: Is approved by the US FDA for adjunctive therapy of Parkinson's disease, but not for hyperprolactinemia (the initial patent holder never submitted the necessary formal studies to support this indication, and a generic formulation is now available). Despite this, many competent endocrinologists have used this drug extensively for this purpose, since it can be taken once daily, is generally better tolerated than bromocryptine, and is dramatically less expensive than either of the other agents (a one month course of 0.25 mg costs only \$59.00). Because of the marked cost reduction and tolerability, I have personally used this as my preferred agent for the past 20 years, and have been quite pleased with the initial and sustained response experienced by most patients. However, it should be noted that the FDA has received

about 15 reports of valvular heart disease in patients taking pergolide, with lesions histologically similar to those associated with other ergot derivatives as well as fenfluramine. Although a causal relationship has not been established, this very rare association has caused some physicians to avoid using pergolide for this purpose.

Quinagolide: Is a non-ergot dopamine agonist that can be given once daily, with tolerance and efficacy similar to bromocriptine. It is not available in the United States.

Estrogen: Is a reasonable alternative for patients who have symptomatic hypogonadism, do not desire fertility, and have minimal galactorrhea. It is very important to monitor prolactin levels carefully, since some cases of tumor enlargement during estrogen therapy have been reported.

Once prolactin levels have been returned to normal on pharmacologic therapy, the dose of dopamine agonist can gradually be reduced in many patients without the recurrence of hyperprolactinemia. Several studies have even shown that between 15-35% of patients will maintain normal prolactin levels for at least several years after completely discontinuing dopamine agonist therapy. As would be expected, recurrence is more likely if a radiographic remnant is still visualized at the time therapy is stopped.

Transsphenoidal surgery: Is occasionally necessary for lactotroph tumors, usually when a patient either fails to respond to or cannot tolerate dopamine agonist thera-

py. Another rare situation which warrants serious consideration of surgery is a pre-menopausal woman who has a massive macroadenoma and desires to become pregnant, since the tumor might enlarge significantly during pregnancy, particularly if the medication is stopped. In general, however, surgery is not preferred for lactotroph tumors, due to their relatively high rate of recurrence (40-50% within 5 years).

External radiation therapy: Is of very limited benefit in the treatment of lactotroph tumors, since the response is typically quite modest and delayed, with prolactin levels often remaining elevated many years after treatment. It is used primarily for adjunctive therapy of prolactin-secreting macroadenomas that have required surgical debulking, in the hopes that regrowth will be prevented. Patients should be counseled that such treatment carries a 50% risk of developing loss of other anterior pituitary hormonal function over the next ten years.

In summary, hyperprolactinemia is a common cause of sexual and reproductive dysfunction. A careful evaluation will almost always discover the underlying etiology, and currently available therapeutic options allow the clinician to successfully treat the condition in the vast majority of patients. Data on the use of dopamine agonists during pregnancy are quite limited, and further studies in this area are warranted.