Prolactinomas
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INTRODUCTION
Hyperprolactinemia is an important cause of galactorrhea, irregular menses, and infertility, especially among young women. The prolactin (PRL)-secreting pituitary adenoma (prolactinoma) is the most common pathologic cause of hyperprolactinemia. In patients harboring macroprolactinomas, besides hypogonadism-related symptoms, mass effect symptoms, such as other pituitary deficiencies and headache and visual disturbances, can also be found.

Besides prolactinomas, physiologic (pregnancy and lactation), pharmacologic (especially antipsychotics), systemic diseases (renal and hepatic failure), endocrine diseases (hypothyroidism, Cushing disease), other pituitary or sellar region tumors causing pituitary stalk disconnection, and macroprolactinemia can be the cause of hyperprolactinemia. More recently, PRL receptor mutation was described as a cause of hyperprolactinemia. Idiopathic hyperprolactinemia is diagnosed after ruling out all referred causes.

The identification of the correct cause of hyperprolactinemia is crucial for treatment. For example, in pharmacologic hyperprolactinemia, this can be achieved by discontinuing or switching the suspected drug. Concerning prolactinomas, dopamine agonist (DA) is the specific treatment of choice in most cases.

KEYWORDS
• Hyperprolactinemia • Prolactinoma • Pituitary tumors
• Hypogonadotropic hypogonadism • Infertility • Prolactin • Dopaminergic agonists

KEY POINTS
• Hyperprolactinemia is an important cause of infertility.
• Prolactinomas are the main pathologic cause of hyperprolactinemia.
• Medical treatment with dopamine agonists is effective and safe in most cases.
• Many current and potential future treatments may overcome the burden of aggressive and resistant prolactin-secreting tumors.
EPIDEMIOLOGY

Prolactinoma is the most common pituitary tumor. Its estimated prevalence is 500 cases per million and incidence of 27 cases per million per year. Microadenomas correspond to 60% of the cases prevailing in women. Adolescents and men usually harbor macroadenomas. PRL-secreting carcinomas are extremely rare.1

PATHOPHYSIOLOGY

PRL is under dopaminergic inhibitory tonus coming from tuberoinfundibular-pituitary neurons. Dopamine acts through dopamine receptor type 2, especially the short isoform, reducing PRL transcription and secretion, and reducing lactotroph proliferation.2 However, various factors stimulate PRL secretion by inhibiting dopamine tonus, such as opioids, cholecystokinin, bombesin, neurotensin, and neuropeptide Y; or by directly stimulating PRL secretion, such as vasoactive intestinal peptide, breastfeeding, and stress.3 Estrogens stimulate PRL secretion acting directly in the lactotrophs and also reducing dopaminergic activity by increasing expression of the less active long isoform of the D2 receptor.2 Hyperprolactinemia causes hypogonadism mainly by inhibiting pulsatile gonadotropin-releasing hormone secretion, in addition to direct inhibition of gonadal steroidogenesis.4 It was recently demonstrated in rodents that PRL directly acts on hypothalamic neurons by inhibiting the expression of the gene Kiss1 kisspeptin, and this could be the possible mechanism responsible for reducing secretion of gonadotropin-releasing hormone.5 Signs and symptoms related to hyperprolactinemia are present in physiologic states, such as pregnancy and breastfeeding, and in pharmacologic and pathologic cases.

CLINICAL FEATURES

Signs and symptoms found in patients with hyperprolactinemia are related to hypogonadotropic hypogonadism and galactorrhea. Galactorrhea is not a specific signal and may be present in individuals with normal PRL levels.6 Hypogonadism can cause menstrual irregularity and amenorrhea in women, sexual dysfunction, infertility, and loss of bone mineral mass in both genders. Hyperprolactinemia is an important cause of infertility in clinical practice. In women, it can be characterized by short luteal phase, anovulatory cycles, oligomenorrhea, and amenorrhea, whereas in men, changes in viability and quantity of sperm can occur.7 Hyperprolactinemia can also reduce libido independently of testosterone levels.8,9 Patients with hyperprolactinemia often have reduced bone mineral density,10 which may lead to fractures in both sexes. In patients with macroprolactinomas, besides the implications related to hormonal hypersecretion, tumor mass effect symptoms, such as headache, visual changes, and hydrocephalus, can also occur. Hypopituitarism beyond hypogonadism can occur if there is compression of the pituitary stalk or destruction of normal pituitary tissue.11,12

DIAGNOSIS

In patients with signs and symptoms related to hyperprolactinemia, evaluation of serum PRL is required. Usually, in prolactinomas, PRL level is proportional to the tumor mass: 50 to 300 ng/mL in microprolactinomas and 200 to 5000 ng/mL in macroprolactinomas (normal range, 2–23 ng/mL). However, disproportion between PRL levels and tumor mass can be found in cystic prolactinomas and giant prolactinomas because of “hook effect” (discussed later). Provocative tests, such as thyrotropin-releasing hormone and metoclopramide, or even suppression test with L-dopa are
no longer used in clinical practice because they do not help the differential diagnosis. In pituitary tumors, except for prolactinomas, and in other tumors of the sellar region, pituitary stalk disconnection may occur with consequent loss of the inhibitory effect of dopamine in the lactotrophs, resulting in hyperprolactinemia. Nevertheless, PRL levels in those situations rarely exceed 100 ng/mL. The differential diagnosis between prolactinomas and the so-called “pseudoprolactinomas” is critical to point to the correct treatment, medical for prolactinomas and surgical for other tumors and the clinically nonfunctioning ones.

Giant prolactinomas in general present with extremely high PRL levels, greater than 4000 ng/mL, which can cause a laboratorial artifact in PRL serum measurement by immunometric assays underestimating the real value, known as “hook effect.” Serum dilution can prevent this diagnostic pitfall.

Another cause of clinical and laboratory dissociation is macroprolactinemia. PRL isoforms can be classified according to their molecular weight as monomeric, dimeric, and macroprolactin (big-bigPRL). Typically, the most prevalent isoform is monomeric, followed by dimeric, being macroprolactin less than 5% of total PRL. However, in 10% and 25% of patients with hyperprolactinemia, the major circulating isoform is macroprolactin, a situation known as macroprolactinemia. Macroprolactin, mostly formed by a complex of IgG bound to PRL, has low biologic activity, being macroprolactinemia, a benign condition. However, macroprolactinemia can coexist with elevated serum levels of monomeric PRL, leading to symptomatic hyperprolactinemia. In this situation, additional imaging and laboratory research are required. The screening of macroprolactinemia is routinely performed by dosing serum PRL recovery after treatment with polyethylene glycol.

In a patient with hyperprolactinemia, after excluding pregnancy, breastfeeding, pharmacologic causes, primary hypothyroidism, and renal and hepatic impairment, it is recommended to perform an MRI, which may detect a microprolactinoma (<1 cm) or a macroprolactinoma (>1 cm). Giant prolactinomas are defined when the maximal diameter is greater than 4 cm. If a macroprolactinoma causes optic chiasmal compression, a neuro-ophthalmologic evaluation is indicated. Because hyperprolactinemia can cause hypogonadism and reduced bone mineral density, bone densitometry should be performed and repeated, if necessary.

Additional pituitary function should be assessed, especially in macroprolactinomas, including insulinlike growth factor 1 measurements to evaluate the possibility of tumoral growth hormone (GH) cosecretion. Serum gonadotropin levels may be normal or suppressed, reflecting hypogonadotropic hypogonadism. In patients with prolactinomas, screening for multiple endocrine neoplasia type 1 is also recommended. Because the issue of valvular heart disease associated with the use of DAs for prolactinomas is still an open question, we recommend performing a trans-thoracic echocardiogram before the initiation and periodically depending on the dose and duration of treatment.

**TREATMENT**

Goals of prolactinoma treatment include normalization of serum PRL levels and reduction of tumor size in macroprolactinomas, aiming at eugonadism restoration and regression of mass effects that lead to headache, visual disturbances, and hypopituitarism. Treatment modalities are DA, neurosurgery, and radiotherapy.

DAs are the gold standard treatment of prolactinoma, because its use controls hormonal secretion and tumor growth in about 80% of cases. Cabergoline (CAB), a specific agonist of the D2 receptor, is the first choice because of its greater
efficacy and better tolerability. Bromocriptine use leads to normal serum PRL levels in 80% of microprolactinomas and 70% of macroprolactinomas, whereas with CAB this objective is achieved in 85% of patients. The most common side effects are nausea, vomiting, and postural hypotension. Rarely nasal congestion, cramps, and psychiatric disorders may develop. CAB, in much higher doses than those commonly used in hyperprolactinemia, was related to valvulopathy in patients with Parkinson disease. Because CAB is also an agonist of the serotonin receptor 5HT2B it can promote valvar fibroblasts proliferation and, consequently, valvular insufficiency, especially in tricuspid and pulmonary valves. In patients using CAB for the treatment of hyperprolactinemia, the association with valvular heart disease is still controversial. In a recent review, no risk of valve failure associated with the use of CAB was observed in most studies. Nevertheless, a greater risk of mild to moderate regurgitation usually in tricuspid valve has been reported in some publications, one study reporting moderate risk of dose-dependent tricuspid regurgitation. In recent studies, bromocriptine has also been implicated with subclinical valvular fibrosis, and therefore may not be a safe alternative for patients on CAB with newly diagnosed or preexisting valvular relevant abnormalities. Quinagolide, a nonergot DA only available in Europe, could be an alternative, but no data on this issue are published to date. Although a matter of controversy, we suggest this procedure before and periodically during use of DA, at the physician’s discretion.

Remission of hyperprolactinemia may occur after DA treatment. In a recent meta-analysis, Dekkers and colleagues showed that on average, 21% of patients with microprolactinomas or macroprolactinomas treated with DA maintained normoprolactinemia after drug discontinuation. Therefore, in patients presenting with normoprolactinemia and tumor reduction, it is worth trying to withdraw the drug, especially after 2 years of treatment.

**Surgical Treatment**

Surgery, usually by the transsphenoidal approach, is indicated for patients with resistance or intolerance to DA; macroprolactinomas with chiasmal compression and visual impairment without fast improvement by medical treatment; symptomatic apoplexy; cerebrospinal fluid leak, which can occur in cases of invasion of the sphenoid sinus; and tumor shrinkage with the use of DA. In a recent review, more than 90% of cases of cerebrospinal fluid leakage were related to the use of DA, with a mean time of 3.3 months between the start of drug administration and the diagnosis of rhinorrhea, although it was already reported that this treatment complication can occur during long-term treatment. The experience of the neurosurgeon, moderately increased serum PRL levels (<200 ng/mL), and tumor size and invasiveness are the most important determinants of successful surgical treatment. In a literature review, prolactinoma remission occurred on average in 74.7% and 34% in microprolactinomas and macroprolactinomas, with a recurrence rate of 18% and 23%, respectively. Tumor debulking is a strategy that has been successfully used for other pituitary adenomas, such as somatotropinomas. In two recent studies, the authors showed that many patients with partial resistance to CAB achieve PRL normalization after surgical debulking, using a lower dose of CAB.

**Radiotherapy**

Prolactinomas are among the most radioresistant pituitary tumors. Therefore, radiation therapy is only indicated to control tumor growth in DA-resistant cases not
controlled by surgery. PRL normalization occurs in 31.4% of cases, and there was no difference in efficacy between conventional and stereotactic techniques. Side effects include hypopituitarism, optic nerve injury, neuropsychiatric disorders, cerebrovascular disease, and development of secondary tumors.

**Management of Aggressive Prolactinoma**

Aggressive prolactinomas are characterized by the presence of expansion or invasion of neighboring structures, rapid tumor growth, and/or the presence of a tumor more than 4 cm in diameter. Many of them are resistant to DA. The first strategy to treat patients partially resistant to DA is a gradual increase in the dose of medication. Although the use of more than 2 mg per week of CAB is off label, Ono and colleagues achieved normalization of PRL levels in 96.2% of patients with doses up to 12 mg per week of CAB. Another strategy is the use of temozolomide, an oral alkylating agent that crosses the blood-brain barrier. In a recent review of the literature there was response in 15 of 20 cases of PRL-secreting pituitary adenomas or carcinomas on temozolomide. The response was correlated to the absence of the methylguanine methyltransferase studied by immunohistochemistry. The methylguanine methyltransferase is a DNA repair enzyme that neutralizes the effect of temozolomide chemotherapy, but the influence of this presence as a prognosis factor is still controversial. Other treatment strategies undergoing clinical trials are the use of chimeric molecules (somatostatin analogues and dopamine D2 antagonists); multiligand somatostatin analogs, such as pasireotide; estrogen receptor modulators; PRL receptor antagonists; and antiblastic drugs, such as mTOR and tyrosine kinase inhibitors.

**Prolactinomas, Fertility, and Pregnancy**

Fertility is restored in most women with the use of DA. Nevertheless, in the absence of hormonal control in cases with microprolactinomas, clomiphene citrate or recombinant gonadotropins may be used for ovulation induction. During pregnancy, the primary concern is growth of the tumor, because of high levels of estrogens, leading to visual disturbance and headache. In microprolactinomas, the chance of clinically significant tumor growth is less than 5%, and therefore, after pregnancy confirmation, DA can be withdrawn and the patient should be monitored clinically every trimester. In the presence of headache or visual changes, sellar MRI without gadolinium enhancement should be performed, preferably after the first trimester of pregnancy. If there is a significant tumor growth, DA should be reintroduced. However, in patients with macroadenomas, the risk of tumor growth with clinical repercussion is up to 35%. Thus, in patients with expansive macroadenomas, it is mandatory to observe a tumor within the sellar boundaries, and usually to wait at least 1 year with treatment with DA. When tumor reduction does not occur, surgical treatment is indicated before allowing pregnancy.

The maintenance or not of DA during pregnancy should be a decision of the specialist. Neuro-ophthalmologic assessment should be performed periodically. In a case with tumor growth after DA withdrawal, the initial procedure is the reintroduction of the drug. In case of failure, surgical treatment is indicated, preferably in the second trimester.

In men, in addition to sexual dysfunction, hyperprolactinemia can cause changes in sperm quality, especially in relation to motility. A period of CAB treatment beyond that required for achieving normal levels of testosterone is usually necessary for improving sperm quality. In patients who remain with hypogonadism, clomiphene citrate has proved useful in increasing testosterone levels, even in the absence of normal serum
PRL levels. This approach has advantages over testosterone replacement regarding fertility restoration.44

MANAGEMENT

In a patient with signs and symptoms related to hyperprolactinemia, serum PRL levels must be performed and after hyperprolactinemia confirmation, clinical and laboratorial work-up to identify possible causes is necessary. After ruling out pregnancy, lactation, drug-related hyperprolactinemia, renal or hepatic insufficiency, and hypothyroidism, a sellar MRI is indicated. In general, in patients with microprolactinomas and especially macroprolactinomas, DA use could be introduced gradually. Except when pregnancy is desired, CAB is the preferential choice.45 The dose can be titrated slowly, according to serum PRL levels monthly to every three months, from 0.25 mg once or twice a week to 2 mg a week. If there is visual deficiency, a new evaluation can be performed in days or weeks. Sellar MRI should be repeated depending on tumor characteristics at the physician’s discretion.

REFERENCES


