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Pathogenesis, diagnosis and current treatment of prolactinoma: a review of the literature

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ABSTRACT:
Prolactinoma is a benign tumor of the pituitary gland that leads to the overproduction of prolactin. It is the most common type of pituitary adenoma, accounting for approximately 50% of all pituitary tumors. The clinical presentation of prolactinoma varies depending on the level of prolactin elevation and the size of the tumor. In women, common symptoms include galactorrhea, amenorrhea, and infertility. Men may present with hypogonadism, decreased libido, erectile dysfunction, and gynecomastia. Large prolactinomas, known as macroadenomas, can cause mass effects such as headaches, visual disturbances due to compression of the optic chiasm, and hypopituitarism due to pressure on surrounding pituitary tissue. Understanding the pathogenesis of prolactinoma is crucial for developing effective treatments and improving patient outcomes. The development of prolactinomas involves a complex interplay of genetic, hormonal, and cellular factors.

Treatment of prolactinoma aims to normalize prolactin levels, reduce tumor size, and alleviate symptoms. The first-line therapy is dopamine agonists, such as cabergoline and bromocriptine, with surgery and radiotherapy reserved for refractory cases. Furthermore, chemotherapeutic agent - temozolomide may be a treatment of choice in aggressive or malignant prolactinomas. By understanding the underlying mechanisms and different treatment methods, healthcare providers can optimize the management and outcomes for patients with prolactinoma.

AIM OF THE STUDY

The aim of this review is to update the recent advances in understanding the pathogenesis, diagnosis, and treatment of prolactinoma. By comprehending the underlying mechanisms and different treatment methods, healthcare providers can optimize the management and outcomes for patients who suffer from this condition.

MATERIALS AND METHODS

This article is the result of a review of recent scientific literature obtained from PubMed and Google Scholar databases using the following keywords: “prolactinoma pathogenesis”, “prolactinoma treatment”, “dopamine agonists”, “cabergoline”, “bromocriptine”, “temozolomide”

CONCLUSIONS

For clinicians, a thorough understanding of prolactinoma pathogenesis, coupled with an evidence-based approach to diagnosis and treatment, is essential for managing this condition. Regular monitoring and follow-up are crucial for assessing treatment efficacy, detecting recurrence, and managing any long-term complications. Interdisciplinary collaboration among endocrinologists, neurosurgeons, radiologists, and other healthcare providers is key to providing comprehensive care for patients with prolactinoma. Continued research and innovation in this field will undoubtedly lead to even better management strategies, ultimately improving the quality of life for those affected by this condition.

KEY WORDS: “prolactinoma pathogenesis”; “prolactinoma treatment”; “dopamine agonists”; “cabergoline”; “bromocriptine”; “temozolomide”

INTRODUCTION

Prolactinomas are the most common type of pituitary tumor, with microprolactinomas being more common in women and macroprolactinomas more frequent in men. Hyperprolactinemia is a leading cause of hypogonadotropic hypogonadism in both sexes, leading individuals to seek medical advice for symptoms such as infertility, oligo-amenorrhea, impotence, and osteoporosis/osteopenia. In men, it often presents with symptoms related to mass effects, including hypopituitarism, visual loss, compression of the optic chiasm, cranial nerve deficits, and headaches. The diagnostic process typically involves a single prolactin (PRL) measurement and pituitary imaging. Dopamine agonists (DA), particularly cabergoline, are the preferred treatment for prolactinomas. These medications can control the disease, restore fertility in both sexes, and permanently cure approximately one-third of patients, allowing them to discontinue treatment. In women, pregnancy and menopause can lead to a natural decline in prolactin levels, potentially allowing for earlier discontinuation of cabergoline.

Surgery and/or radiotherapy are considered for patients who are resistant to cabergoline, especially when increasing the dosage to the maximum tolerated level does not overcome resistance, or when the patient opts for surgery. Resistance to cabergoline in invasive and proliferative tumors may indicate biological aggressiveness, necessitating alternative treatments, often involving temozolomide either as a monotherapy or in combination with radiotherapy. [1,2] We would like to present the current knowledge of the pathogenesis and diagnosis of prolactinomas and outline the potential treatment options that align with evidence-based medical standards. Furthermore, we would like to emphasize challenging clinical cases where standard treatment is ineffective due to the tumor being resistant and aggressive.

EPIDEMIOLOGY

Prolactinomas account for approximately 50% of all clinically recognized pituitary adenomas. [3,4] The average prevalence of prolactinoma is estimated at 10 per 100,000 men and 30 per 100,000 women, with the highest prevalence in women aged 25 to 34 years compared to men, while this difference disappears after menopause. [5-10] Among prolactinoma patients, around 60% of men have macroprolactinomas, whereas 90% of women have microprolactinomas. [11] Moreover, the standard annual incidence rate of prolactinomas ranged from 2 to 5 new cases/100,000, and the value is 3 times higher in women than in men. [10,12-15] Recent epidemiological studies conducted in various countries have revealed that the prevalence of pituitary adenomas needing medical intervention is significantly higher than previously estimated. Prolactinomas consistently emerged as the most common tumor subtype [10, 12, 13, 16-21]. The overall prevalence of prolactin-secreting tumors ranged from 25 to 63 per 100,000 people. Symptomatic microprolactinomas have a prevalence of about 40 per 100,000, while macroprolactinomas are approximately 10 per 100,000.

PATHOGENESIS

Most prolactinomas are sporadic, with familial cases being quite rare. When they do occur, they are often associated with conditions like Multiple Endocrine Neoplasia type 1 (MEN1) or Familial Isolated Pituitary Adenoma Syndrome. For young patients with macroprolactinomas, genetic testing typically includes screening for MEN1 and AIP gene mutations, and less commonly, MEN4, MEN5, or those associated with paragangliomas. Like other pituitary adenomas, prolactinomas originate from a single mutated lactotroph cell that undergoes monoclonal proliferation. Researchers have investigated various somatic genetic alterations that could be involved in the development and progression of prolactinomas. However, aside from a recently identified somatic mutation in the splicing factor 3 subunit B1 (SF3B1) gene found in about 20% of over 200 surgically removed prolactinomas (though this finding awaits independent confirmation), no specific mutations have been identified that account for more than a small number of cases. [22,23] The pathogenesis of prolactinoma without the SF3B1 mutation remains unclear. One of the primary factors driving the development of lactotroph tumorigenesis is estrogen, but this mechanism is not well characterized and requires further research. [24]

DIAGNOSIS

The diagnosis of prolactinoma is typically based on the simultaneous observation of persistent hyperprolactinemia and the presence of a pituitary adenoma on magnetic resonance imaging (MRI), showing a good correlation between hormone levels and tumor size. [7] Confirmation by immunocytochemistry is rare because most prolactinomas are not surgically removed. Macroprolactinomas are usually identifiable with high confidence when prolactin levels exceed 200 μg/L (4,200 mU/L). In patients with histologically confirmed non-functioning pituitary macroadenoma and stalk compression, prolactin levels generally remain below 150 μg/L. [25] In cases of uncertainty, such as when there is a mismatch between tumor size and prolactin levels, or in cystic or necrotic pituitary macroadenomas with intermediate prolactin levels between 100 and 200 μg/L, a 3- to 6-month trial with a dopamine agonist can be useful, as most prolactinomas will reduce in size under medical therapy. The thyrotropin-releasing hormone stimulation test is typically not useful in these situations. [26,27,28] Clinicians may have more difficulties in formally confirming the diagnosis of a microprolactinoma. Symptoms of hyperprolactinemia are nonspecific and can arise from various causes other than tumors. MRI results may not always clearly indicate the presence of a pituitary adenoma, especially when non-functional pituitary incidentalomas are common. Moderate hyperprolactinemia can also be caused by medications, a condition frequently encountered, and it's crucial to test for the presence of macroprolactin in patients with asymptomatic hyperprolactinemia. [29] Most microprolactinomas, however, typically present with symptoms, appear as a distinct lateral nodule with a different T1 or T2 intensity on dedicated MRI scans compared to normal pituitary tissue, and show prolactin levels above 40 μg/L (twice the upper limit of normal). While the absence of one or more of these criteria does not exclude the diagnosis, clinicians should remain vigilant about other potential causes and consider monitoring or early cessation of dopamine agonist therapy before committing to long-term treatment. Furthermore, if there is a discrepancy between effective hormonal control with DA therapy and continued tumor growth, reassessment of the diagnosis is essential. [26]

TREATMENT

The goals of treating prolactinomas are to restore normal gonadal function and fertility; and to reduce tumor size in patients with macroadenomas. For patients who have minimal symptoms and have normal MRI scans or microadenomas, observation alone may be sufficient. In these cases, prolactin levels should be monitored every 6 to 12 months. If prolactin levels increase or symptoms related to hyperprolactinemia develop, a repeat MRI may be performed to evaluate tumor size and determine if treatment is needed. [29,30] Only 5% to 10% of microprolactinomas enlarge over 10 years. [27] Dopamine agonists are in most cases the first-line treatment, while surgery is typically considered a secondary option. Aggressive prolactinomas should be treated with multimodal therapy, which includes high-dose cabergoline, surgery, radiation therapy, and temozolomide. [31]

Dopamine agonists

Pharmacotherapy is the primary treatment for prolactinomas, with dopamine agonists being the main therapy for nearly all prolactinomas, regardless of size.

This includes microtumors (less than 1 cm in diameter), macrotumors (greater than 1 cm), and giant tumors (greater than 4 cm). DAs, such as bromocriptine, cabergoline, or quinagolide, are highly effective in reducing prolactin secretion and shrinking tumor size. [24, 29] Bromocriptine was the preferred treatment until the emergence of cabergoline in the late 1980s and early 1990s. [32] The normalization rate of serum PRL with bromocriptine was 78% for patients with microtumors and 72% for those with macrotumors. [27] Cabergoline has proven to be highly effective in normalizing serum PRL levels and reducing tumor size. Among female patients treated with cabergoline, 83% achieved normalized PRL levels, 72% experienced a return of their menstrual cycle, and only 3% discontinued due to adverse effects. In comparison, 59% of those treated with bromocriptine achieved normalized PRL levels, 52% had their menstrual cycle restored, and 12% discontinued due to adverse effects. [33] Another study showed that cabergoline normalized PRL levels in 92% of patients with microprolactinomas and 77% of patients with macroprolactinomas. [34] A large comparative study found that patients who had not previously been treated with dopamine agonists experienced greater tumor shrinkage on lower doses of cabergoline than those who had been treated with other DAs like bromocriptine or quinagolide.

This included patients who were previously responsive, intolerant, or resistant to other DAs. [35] In treating macroprolactinomas, cabergoline proved to be more effective than other DAs, both in normalizing prolactin levels and reducing tumor size. [36] As mentioned earlier, men typically have larger and more resistant prolactinomas compared to women. Specific studies have shown that cabergoline is effective in male patients, particularly in restoring sexual function and improving semen analysis. [37]

Bromocriptine is an ergot derivative that functions as both a D1R and D2R agonist. It is typically started at a dose of 1.25–2.5 mg daily, which can be increased to twice daily as needed. Doses can go up to 30 mg/day, divided into two doses. Although bromocriptine is infrequently used today, some experts still recommend it for women seeking pregnancy due to the extensive data supporting its safety during pregnancy and who live in countries where cabergoline use for this purpose is not approved. [38] Furthermore, it may be continued in patients whose symptoms have been effectively managed by this drug for an extended period or in patients with significant cardiac valve disease. [10]

Cabergoline is an ergot derivative that is more (but not strictly) selective for D2R and has a long duration of action, which permits once or twice weekly administration. Treatment most often starts with low doses of 0.25 mg twice weekly, preferably taken in the evening after a meal to reduce gastrointestinal side effects, particularly nausea. For microadenomas, a standard starting dose ranges from 0.5 to 1 mg per week. If serum prolactin levels do not normalize within 6–8 weeks, the dose may be increased. Similarly, for macroprolactinomas, an initial dose in this range may be used, with potential escalation to 1 mg twice weekly by the third week. In cases where there is suprasellar extension causing visual field defects, the dose may be escalated more rapidly to 1 mg twice weekly by the beginning of the second week. A prolactinoma is typically considered resistant if prolactin levels do not normalize after reaching a dose of 2 mg per week of cabergoline. [39]

Quinagolide is a non-ergot dopamine agonist that specifically targets D2 receptors.

Typical therapeutic doses range from 0.075 to 0.600 mg once daily. Its effectiveness in normalizing prolactin levels and reducing tumor size is comparable to bromocriptine. [27,40] Moreover, around 40% of patients who do not respond to bromocriptine show improvement with quinagolide [41]. Adverse effects are less common compared to bromocriptine, likely due to its higher specificity for D2 receptors and lack of intrinsic agonist activity towards 5-HT2B receptors. [27,40]

All dopamine agonists, even when taken at low doses, can cause various side effects such as nausea, vomiting, other gastrointestinal symptoms, orthostatic hypotension, fatigue, headache, nasal congestion, and Raynaud's phenomenon [27,29]. These short-term effects are associated with the simultaneous activation of 5-HT1 receptors and D1 receptors, and they occur more frequently with bromocriptine compared to cabergoline or quinagolide. [33,42] These side effects can be reduced by starting the medication at a low dose before bedtime, taking it with meals, and gradually increasing the dosage. In 2007, two studies reported an elevated risk of cardiac valve disease linked to high-dose cabergoline therapy in Parkinson’s disease. [43,44] The cumulative dose of cabergoline associated with these valve abnormalities (such as fibrotic thickening and stiffening of the leaflets, chordae, and a reduction of the valve tenting area) in these studies was significantly higher than the doses typically used for treating prolactinomas.

More concerning are neuropsychiatric symptoms like psychosis and impulse control disorders (ICDs), such as pathological gambling, hypersexuality, compulsive buying or eating, and punding. ICDs have been observed in association with bromocriptine, quinagolide, and cabergoline treatments and there is no good evidence to suggest that changing DA will alleviate symptoms. Only discontinuing DAs usually reverses these side effects. [2,45,46] If a patient demonstrates intolerance to all available dopamine agonists, alternative treatments such as neurosurgery should be considered.

Surgery and radiotherapy

Neurosurgical treatment of prolactinomas is less effective than medical therapy, with a high recurrence rate of hyperprolactinemia (10-50% of patients). However, transsphenoidal surgery should be considered as second-line therapy for symptomatic patients who cannot tolerate any of the available DAs or who do not respond to the maximum tolerated doses of these medications. [47] Furthermore, surgery had a role in treating acute complications such as pituitary apoplexy or cerebrospinal fluid leakage. Debulking surgery may be considered for women with macroprolactinomas who are planning to become pregnant. Other recently seen indications are young patients with a high probability of complete tumor removal who prefer not to undergo long-term medical treatment, or patients with predominantly cystic tumors. [10]

Most surgeries for prolactinomas are conducted via transsphenoidal surgery, with endoscopic transsphenoidal surgery being the predominant technique. A craniotomy may be necessary depending on the tumor's location. A meta-analysis revealed that remission rates were comparable between patients who had endoscopic surgery and those who underwent microscopic surgery. [10,48]

The success of surgery largely depends on the neurosurgeon's experience and skill, as well as the tumor's size and invasiveness. Remission rates were higher in centers with a high number of surgical cases compared to those with a small number. [49]

Because medical treatments are highly effective in managing symptoms for most patients and surgery can quickly alleviate acute complications, radiotherapy (RT) is now rarely used for prolactinomas. It should be reserved for the uncommon cases of large tumors that do not respond to dopamine agonists, recur or progress after surgery, and exhibit high aggression or malignancy. [5]

Temozolomide

The primary adjunct medical therapy for treating aggressive prolactinomas and metastatic pituitary neuroendocrine tumors (PitNETs) has been temozolomide [50]. This lipophilic oral alkylating agent, which can cross the blood-brain barrier, is commonly used to treat glioblastoma [51]. Its use for PitNETs began in 2006 [52], and since then, aggressive prolactinomas have become the second most common PitNET treated with it. The standard dose is 150–200 mg/m2 for the next 5 days every 4 weeks. While most patients have received a standard 6–12 month course, longer courses of 2 years or more are now recommended [50]. Tumor size reduction is seen in over 50% of cases, and responders show evidence of prolonged survival [53].

CONCLUSIONS

Prolactinomas exhibit significant biological diversity, ranging from small, slow-growing microadenomas to large, invasive macroadenomas, and in rare cases, aggressive metastatic cancers. They are the most responsive PitNET to medical treatment and the majority of patients can be treated successfully with dopamine agonists. While prolactinoma diagnosis is generally straightforward and treatment guidelines are well-established, several challenging issues persist in their management. Prolonged use of dopamine agonists may not be appropriate if the diagnosis of prolactinoma is not adequately confirmed. Moreover, the appropriate timing for discontinuing dopamine agonist treatment and the current indications for transsphenoidal surgery are still under discussion. Furthermore, managing resistant or aggressive prolactinomas, particularly in young patients, continues to pose a significant challenge for clinicians and should be managed via a multidisciplinary team.

Disclosures

The authors do not report any disclosures.

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