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Prolactinoma: Medical and Surgical Considerations

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KEYWORDS

• Prolactinoma • Pituitary tumor • Surgical considerations • Dopaminergic therapy • Transsphenoidal surgery • Prolactin

KEY POINTS

- The mainstay of prolactinoma management is medical therapy with dopamine agonists (DA).
- Surgical intervention should be considered for patients who fail to respond to DA therapy, cannot tolerate DA therapy, or have macroadenomas with a large cystic component.
- Pituitary apoplexy with sudden visual decline secondary to optic nerve compression is a surgical emergency.
- Radiation therapy is most commonly used as an adjunctive or second-line treatment.
- Whether medical or surgical interventions are pursued, long-term surveillance via endocrinologic laboratory assessment and MRI is essential.

INTRODUCTION

Prolactinomas are the most common pathologic cause of hyperprolactinemia,[1] and the most common secretory tumor of the pituitary gland.[2] Prolactinomas are histologically benign and arise from monoclonal expansion of pituitary lactotrophs that have undergone somatic mutation. The most commonly implicated genes include pituitary tumor transforming gene and fibroblast growth factor 4.[3] Most prolactinomas arise from sporadic mutations, but they may also occur in concert with certain familial syndromes, such as multiple endocrine neoplasia type 1.

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Symptoms at the time of presentation are either due to regional mass effect or from systemic effects of prolactin hypersecretion.[4,5] Macroadenomas, defined as greater than 10 mm, may become symptomatic via direct compression on the optic apparatus, cavernous sinus, cranial nerves, and normal pituitary gland. Microadenomas, defined as less than 10 mm, are less likely to have symptoms from direct mass effect but instead from supraphysiologic levels of prolactin that suppress the hypothalamic-pituitary (HPA) axis.

CLINICAL PRESENTATION

Regarding macroprolactinomas, presenting symptoms are usually due to mass effect and/or hyperprolactinemia. Symptoms or sequelae related to mass effect include headaches, visual deficits, cranial neuropathies, hydrocephalus, and pituitary apoplexy. Hyperprolactinemia symptoms are generally due to hormonal dysfunction along the HPA axis. In men, this may include decreased libido and impotence. In women, one may see aberrations with menstruation, infertility, or galactorrhea. Pediatric patients may present with pubertal delay, growth arrest, or primary amenorrhea.

DIAGNOSTIC WORKUP

Laboratory assessment for suspected prolactinoma begins with a serum prolactin level. Although prolactinoma is the most common cause of hyperprolactinemia, other causes include pregnancy, medication side effects, hypothyroidism, or other causes of mass effect on the pituitary stalk.[6] Regarding hyperprolactinemia in pregnancy and postpartum, prolactin levels normalize within about 6 months after delivery in nursing mothers, and within weeks in nonnursing mothers.[7]

For prolactinomas, although prolactin levels usually correlate with tumor volume, sometimes prolactin levels can be misleading. Prolactin levels can appear falsely low owing to the “hook effect.” This occurs when extremely high serum prolactin saturates both the capture and the signal antibodies used in immunoradiometric and chemiluminescent assays, preventing the binding of the two. The artifact can be avoided by repeating the assay using a 1:100 serum dilution.[8] Macroprolactin poses another potential challenge in interpreting prolactin levels. Macroprolactin is not clinically significant but is a complex of prolactin and immunoglobulin G antibody. This can cause hyperprolactinemia through decreased prolactin clearance. Misdiagnosis can be avoided by pretreating the serum with polyethylene glycol to precipitate the macroprolactin.[9]

In addition to checking prolactin, all other pituitary hormones and other laboratory evaluations may be necessary, especially in macroprolactinomas. Because prolactin elevation can occur in primary hypothyroidism, thyroid-stimulating hormone and free thyroxine (FT4) should be assessed. Renal and hepatic function should also be evaluated, as reduced prolactin clearance may occur in renal or hepatic failure. In amenorrheic women, serum follicle-stimulating hormone should be obtained to rule out primary ovarian failure. In men, serum testosterone should be assessed. Also, of note in giant prolactinomas, cortisol, FT4, and growth hormone (GH) may be low.[10]

It is important to appreciate that a subset of functional adenomas may aberrantly cosecrete multiple hormones or induce hypopituitarism.[11,12] For example, up to 10% of prolactinomas may cosecrete excess GH.[13] Conversely, some pituitary tumors causing acromegaly may coproduce prolactin in addition to GH.[14]

Other considerations include obtaining bone density testing in patients with hypogonadism. Contrasted magnetic resonance imaging (MRI) of the sella is recommended to assess for local tumor extent. Visual field testing should also be performed to assess for compression on the optic apparatus.

MEDICAL CONSIDERATIONS

Medical therapy for prolactinomas is indicated for macroadenomas, enlarging microadenomas, infertility, bothersome galactorrhea, gynecomastia, testosterone deficiency, oligomenorrhea or amenorrhea, acne, and hirsutism. Microprolactinomas do not always require treatment, as the risk of tumor enlargement is low if untreated.[15] Prolactin levels and tumor size on MRI can be used to monitor prolactinomas, although optimal timing of serial prolactin levels and imaging has not been established. Dopaminergic agonists (DAs) are the mainstay of medical treatment for prolactinomas, as most tumors are sensitive to this therapy.

Dopamine Agonists

According to the Endocrine Society clinical guidelines for prolactinoma management, DAs are recommended to lower prolactin levels, decrease tumor size, reverse galactorrhea, and restore gonadal function in both microprolactinomas and macroprolactinomas.[16] In addition, in macroprolactinomas, DAs aim to decrease or stabilize tumor size to prevent or treat optic nerve compression, cranial neuropathies, or headaches.

With some macroprolactinomas, high prolactin levels may decrease significantly without completely normalizing. As long as the tumor is stable without mass effect and other hormone levels are satisfactory or replaced, persistent prolactin elevation is generally not harmful.[17] For patients with visual field compromise, DA doses are increased rapidly with visual field monitoring every 2 to 4 weeks.[17] If visual fields do not normalize and MRI demonstrates chiasmal compression, patients should be referred for neurosurgical consultation.

Some tumors do not show a response to DA therapy despite dose increases. It is speculated that therapeutic resistance is due to reduced dopamine receptor density on the tumor; thus, changing the type of DA may lead to improvement.[18] Lactotroph cells also may express estrogen receptors and may respond to estrogen blockade.[19–21]

The 2 approved DAs in the United States are bromocriptine and cabergoline. Compared with bromocriptine, cabergoline has fewer side effects and has been more effective with longer remission rates.[22,23]

Duration of Dopaminergic Agonist Therapy and Remission Rates

Remission rates after DA therapy withdrawal range from 15% to 80%.[23–25] The following factors are reliable predictors of success and indications for DA withdrawal: treatment duration for more than 24 months, achieving normal prolactin levels, greater than 50% reduction in tumor size, and requirement of low DA maintenance dose.[23] Treatment may also be stopped in postmenopausal women, as tumors rarely grow after menopause. For patients with macroprolactinomas and extrasellar extension or persistent hyperprolactinemia, it is not advisable to stop DA therapy.

Side Effects of Dopaminergic Agonist Therapy

Rarely, pituitary apoplexy may occur spontaneously or during DA therapy and can require surgical intervention.[26] In addition, rapid tumor shrinking on DAs can lead to cerebrospinal fluid (CSF) leak, which could necessitate surgical repair.[27]

There have also been some reports of an association between DA therapy and cardiac valvulopathy.[28] For example, tricuspid regurgitation occurred more frequently in patients taking higher doses of cabergoline than control subjects.[29] However, multiple studies have also shown no association between clinically significant valvulopathy and low-dose DA treatment.[30] Regardless, it is reasonable to obtain baseline echocardiograms at initiation of DA therapy.[16,28]

SURGICAL CONSIDERATIONS

Although medical therapy may be successful in normalizing prolactin levels and managing tumor growth, surgery remains an important therapeutic modality. DA treatment may require years or even lifelong therapy. Even for those who achieve endocrinologic cure, up to 50% to 80% may recur after DA withdrawal or owing to drug resistance.[24,25]

In general, surgical indications include apoplexy, DA nonresponse, or side effects of long-term medical therapy. Surgical intervention for prolactinomas is aimed at reducing tumor mass, decompressing cranial nerves, and resecting any focus of hypersecretory adenoma while preserving the native pituitary gland.

In some select situations, primary surgery may be indicated without a DA trial. First, primary surgery may be indicated for large tumors with rapidly progressing and significant visual loss, as DAs do not produce an immediate effect.[31–34] Another indication for primary surgery would be patient refusal to undergo DA therapy. A third potential indication for upfront surgery is profound hypopituitarism at clinical presentation, as some studies have demonstrated recovery of pituitary function after selective tumor debulking to decompress the pituitary gland.[10,35,36]

Surgical Approach: Advances and Considerations

There have been significant advances in pituitary surgery that have improved surgeons' abilities to control hormonal oversecretion through precise tumor debulking, while preserving normal pituitary function. One of the greatest advancements in pituitary surgery has been the widespread adoption of endonasal endoscopic approaches to resect sellar and extrasellar tumors. Endoscopic technology allows for superior visualization through improved optical technology and angled endoscopic lenses and instrumentation. This has allowed for visualization and resection of tumors that could not be accessed or removed with straight line-of-sight microscopic approaches. For example, sellar tumors with anterior extension along the planum sphenoidale, superior extension into the third ventricle, or lateral extension into the cavernous sinus can all be visualized and resected through endonasal endoscopic approaches, whereas microscopic access to these regions would be significantly more challenging with potentially greater morbidity.[37–39] In addition to improved surgical exposure, endoscopic CSF leak repair techniques have improved significantly over the decades, with 90% to 95% success rates being achieved consistently.[40,41] The reliable success of CSF leak repair has significantly reduced the morbidity of endoscopic pituitary surgery.

The extrasellar extent of pituitary tumors also has implications on surgical approach. Microadenomas and predominantly intrasellar macroadenomas are easily approached via the transsphenoidal route. Although many macroadenomas with extrasellar extension are also resectable through a transsphenoidal approach, there are limits beyond which transcranial approaches may be necessary, depending on tumor size, shape, invasiveness, and proximity to critical neuroanatomical structures. For example, transsphenoidal approaches are limited when there is significant tumor extension lateral to the carotid artery, necessitating a frontotemporal craniotomy.[37] Large tumors encompassing sellar, suprasellar, or other extrasellar compartments may also warrant both transsphenoidal and transcranial approaches.

Cystic Prolactinoma

Cystic prolactinomas are unique in that they are potentially more resistant to DA therapy. Some studies have demonstrated decreased DA receptor concentration in cystic portions of prolactinomas and therefore lower remission rates with DA therapy.[42] A recent case series of 30 cystic prolactinomas treated with primary medical therapy

demonstrated greater than 80% reduction in cyst volume and biochemical remission, but half the patients ultimately required surgery.[43] More evidence is necessary to determine whether medical therapy can adequately reduce the volumetric burden of cystic prolactinomas. Conversely, surgery yields immediate decompression, biochemical cure, and acceptably low recurrence rates.[44,45] In a series of 212 consecutive prolactinomas, primary transsphenoidal surgery achieved an 80% remission rate for cystic prolactinomas, comparable to DA success rates reported in the literature.[31,32,46]

Radiation Therapy

There is a paucity of literature describing radiation therapy as first-line treatment for prolactinoma given the established efficacy of medical and surgical therapy. Most series examining radiotherapy for prolactinoma have suggested its use as a second-line or adjunctive treatment for patients with suboptimal responses to medical treatment, surgery, or a combination of both.[47–49] Adjuvant radiotherapy has resulted in endocrinologic remission in one-third of cases, while causing hypopituitarism in 15% of cases.[47,50,51]

Regarding radiotherapy options for prolactinomas, conventional fractionated radiotherapy has a lower risk of adverse effects, but a slower and less complete response rate. Stereotactic radiosurgery (SRS) for prolactinoma delivers high-dose radiation in fewer fractions with a more robust treatment response, but brings an increased risk of adverse effects.[52] Patients undergoing SRS are at higher risk for developing hypopituitarism (20% of patients by 5 years and 80% by 10–15 years after treatment).[47,53] Of note, endocrinologic response to radiotherapy varies according to the hypersecretory adenoma type with adrenocorticotropic hormone and GH-secreting adenomas exhibiting a remission rate of 50% or greater, whereas remission in prolactinomas is less than 25%.[53]

In some cases, surgical debulking may be performed before radiotherapy while specifically avoiding manipulation of nearby neural tissues. In these scenarios, subtotal surgical debulking may allow for a tumor-free margin around the adjacent radiosensitive neural structures and prevent postoperative radiotherapy-induced damage to these structures (eg, optic chiasm, cranial nerves, and pituitary gland).[54]

IMPORTANT CLINICAL SCENARIOS

Apoplexy

Macroprolactinomas are more likely to present with visual compromise or cranial nerve palsies. When vision loss occurs acutely, as in the example of pituitary apoplexy, urgent surgical decompression is the mainstay of treatment. The hallmark of pituitary apoplexy includes the classic triad of sudden severe headache, visual changes, and altered consciousness secondary to hypopituitarism and adrenal crisis. Apoplectic signs and symptoms are due to hemorrhage and infarction of the pituitary lesion, which lead to sudden mass effect on the pituitary gland.[55] Those with subtle or gradual visual compromise may elect for a trial of medical therapy because 70% to 90% of prolactinomas exhibit some degree of involution within weeks to months after initiating DA therapy.[56] Those who suffer from progressive vision impairment or fail to demonstrate an adequate reduction in tumor size are suitable candidates for surgery. **Fig. 1** shows an MRI scan demonstrating characteristic imaging features of pituitary apoplexy in the setting of a pituitary macroadenoma.

Dopamine Agonist-Induced Cerebrospinal Fluid Rhinorrhea

Although DA therapy remains the mainstay of primary prolactinoma treatment, approximately 6% of these patients develop CSF rhinorrhea as a consequence of

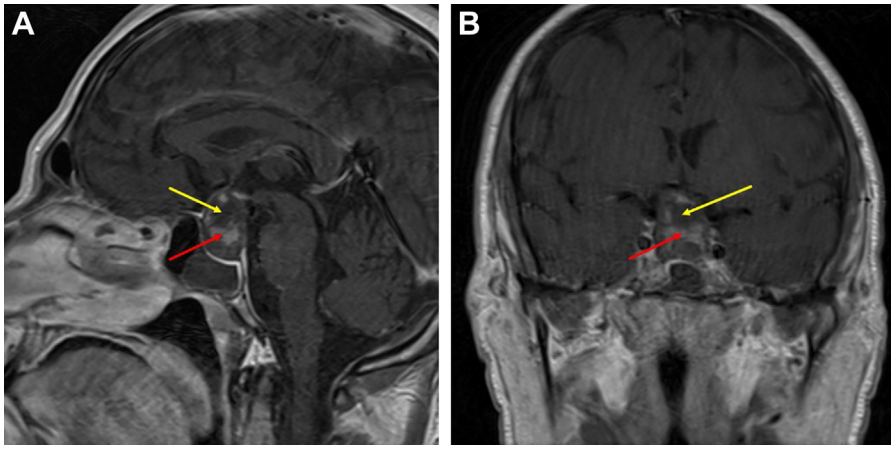

Fig. 1. Apoplexy case example. (*A*) Sagittal and (*B*) coronal MRI T1 scan with contrast images demonstrating a macroprolactinoma with suprasellar extension and acute hemorrhage within the tumor. The pituitary tumor extended superiorly to compress the optic chiasm and abutted the floor of the third ventricle. The sella demonstrated heterogeneous intensities, with enhancing areas of macroadenoma (*red arrows*) and isointense areas representing hemorrhage (*yellow arrows*).

tumor involution in the setting of dural and bony defects of the skull base.[5,57] Macroprolactinomas that exhibit osseous erosion through the sphenoid sinus are at higher risk for developing DA-induced CSF rhinorrhea. Interestingly, the following features have not been associated with CSF leaks after initiating DA therapy: pretreatment tumor size, rate of tumor shrinkage, serum prolactin levels, and rapidity of prolactin reduction.[5,57] The presence of CSF rhinorrhea substantially increases the risk of meningitis and pneumocephalus,[58] and patients should be educated about the signs and symptoms of CSF rhinorrhea and its complications. Importantly, clinicians should collect and test any thin clear nasal drainage for beta-2 transferrin,[59] and if CSF rhinorrhea is confirmed, high-resolution computed tomography imaging of the skull base should be obtained to localize the bony defect in the skull base. Patients should also be referred to surgeons who perform endoscopic CSF leak repair.

SUMMARY

Prolactinomas represent the most common secretory tumor of the pituitary gland. Clinical presentation may be due to prolactin oversecretion, localized mass effect, or a combination of both. The mainstay of prolactinoma management is medical therapy with dopamine agonists, such as bromocriptine and cabergoline. Endoscopic endonasal or transcranial surgery, radiation therapy, or a combination of these is an important treatment option in select cases. Pituitary apoplexy and dopamine agonist–induced CSF rhinorrhea are important clinical considerations in the management of these lesions.

CLINICS CARE POINTS

- Surgical intervention should be considered for patients who fail to respond to dopaminergic agonist therapy, cannot tolerate dopaminergic agonist therapy, or have macroadenomas with a large cystic component.

- Pituitary apoplexy with sudden visual decline secondary to optic nerve compression is a surgical emergency.
- Radiation therapy is most commonly used as an adjunctive or second-line treatment.
- Whether medical or surgical interventions are pursued, long-term surveillance via endocrinologic laboratory assessment and MRI is essential.
- If cerebrospinal fluid rhinorrhea is detected, high-resolution computed tomography imaging of the skull base should be obtained to localize the osseous defect.

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