Giant Prolactinomas

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Abstract

Prolactin-secreting adenomas (prolactinomas) are the most common secreting adenomas of the pituitary. Microprolactinomas (diameter <10 mm) are frequently diagnosed in women, whereas macroprolactinomas (maximum diameter ≥ 10 mm) are generally seen in men. Most macroprolactinomas measure between 10 and 40 mm. Giant prolactinomas, measuring >40 mm, are rare, accounting for only 1–5% of all prolactinomas. Although generally benign, giant prolactinomas are aggressive and invasive, extending into the suprasellar region and also involving the cavernous sinuses. The optic chiasm is frequently involved, which leads to visual damage, and patients occasionally suffer from ophthalmoplegia. Long-term (usually lifetime) therapy with high-dose dopamine agonists (cabergoline or bromocriptine), together with pituitary surgery in some cases and radiotherapy if required, can achieve biochemical remission, tumor control, and clinical improvement in most patients.

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Introduction

Prolactinomas are the most common hormonally active pituitary tumors (~40% of all pituitary adenomas) with a prevalence of ~5 per 10,000 population according to epidemiological surveys [1]. They are classified on the basis of size as microprolactinomas (<10 mm diameter) and macroprolactinomas (≥ 10 mm diameter). Microprolactinomas are usually seen in women, whereas macroprolactinomas have a male predominance [2, 3]. The majority of macroprolactinomas measure 10–40 mm. Tumors measuring >40 mm, termed giant prolactinomas, are rarer, accounting for only 1–5% of all prolactinomas [4, 5]. Giant prolactinomas are usually diagnosed in the 20- to 50-year age group (median 42) in men [4] and occasionally in older or postmenopausal women [6], with a reported male-to-female ratio of ~9:1 [5]. Patients present with prolactin levels above 1,000 ng/mL (21,000 mU/L), and usually up to 100,000 ng/mL. Most have hypogonadism associated with low testosterone levels, and some have at least partial hypopituitarism. Most giant prolactinomas are invasive, with suprasellar extension leading to chiasmal compression and involvement of the ventricular system, and parasellar extension into the cavernous sinus and rarely to the temporal lobe (Fig. 1). They may also extend inferiorly into the sphenoid sinus and

Fig. 1. Coronal MRI T1-weighted sequence, gadolinium enhanced, of two patients with giant prolactinomas at presentation and following cabergoline treatment.

clivus and, rarely, posteriorly into the brainstem. Although the imaging (CT and MRI) appearance of these tumors, especially those larger than 60 mm, suggests a malignant neoplasm not necessarily of pituitary origin, giant prolactinomas are benign and treatable, with similar histological and clinical characteristics to the smaller macroprolactinomas. Only rarely do they carry predictive markers for malignant potential or develop into malignant prolactin-secreting carcinomas. In pituitary tumors, the only suggested proliferation marker of invasiveness and possible malignancy to date is a high Ki-67 labelling

index (>10%). Besides prolactin, a minority of giant prolactinomas express and also secrete growth hormone [7]; co-secretion of other pituitary hormones, mainly thyroid-stimulating hormone, has been reported as well.

Treatment goals for giant prolactinomas are the same as for the more common and smaller macroprolactinomas, including normalization or at least substantial suppression of prolactin level, tumor shrinkage with relief of compression of adjacent structures, particularly the optic chiasm (causing visual field damage) and cranial nerves (causing ophthalmoplegia), increase/normalization of

Table 1. Response to medical treatment with dopamine agonists based on prolactinoma size

Adenoma size	Gender	Visual damage	Surgery	PRL normalized	Testosterone normalized	Ref.
Microadenomas	F > M	None	Rare	80–95%	90%	[3]
Macroadenomas	F = M	40–50%	5–10%	75–90%	55–70%	[3]
Giant prolactinomas >40 mm	M:F – 9:1	70%	15%	60–68%	40–67%	[4, 5, 21]
Giant prolactinomas >60 mm	M:F – 9:1	80%	50%	61%	37%	[7]

testosterone level (to achieve eugonadism and improve reproductive potential), and recovery of altered pituitary axes [8]. However, if the tumor is particularly large and there is long-standing damage to the visual tracts or pituitary hormone function, visual recovery or restoration of gonadal function may not be realistic.

Clinical Symptoms

Men may complain of hypogonadism, erectile dysfunction, visual problems, weakness, and headaches. Galactorrhea is rare. Symptoms in men are typically missed for a long time, sometimes even years, before a diagnosis is made. Women may present with primary or secondary amenorrhea, headaches, and visual deterioration, and in the younger age group, galactorrhea. Long-standing hypopituitarism is reported occasionally. Patients, especially elderly, may be diagnosed incidentally by CT or MRI performed for unrelated reasons. When the giant prolactinoma extends into surrounding cerebral structures, the resulting neurologic and cognitive deterioration may lead to such atypical symptoms as frontal behavioral changes [9, 10], disorientation, reversible dementia [11], hemiparesis, olfactory hallucinations, and temporal epilepsy [12]. Other symptoms that may accompany giant prolactinomas include CSF rhinorrhea, nasal congestion and epistaxis, exophthalmus [13], and cranial nerve palsies (III, IV, V, VI) with ophthalmoplegia and obstructive hydrocephalus [14]. Intensive treatment can be efficacious and reverse these symptoms.

Medical Treatment

Giant prolactinomas have been reported and characterized in the literature in small series by several groups, including ours [5, 15–18]. In the past, the primary treatment was pituitary surgery for immediate relief of the vi-

sual and neurologic symptoms [19]. However, surgery has since been replaced by medical treatment with dopamine agonists, originally bromocriptine and currently cabergoline, as the first-line option. Treatment with dopamine agonists has been found to lead to rapid and striking tumor shrinkage, with possible significant visual improvement within a short period of time, even in patients with complicated giant prolactinomas.

In general, medically treated prolactinomas have a high remission rate of 90% [3]. When they are large and extend outside the sellar borders, the rate of prolactin normalization decreases to 70–80% for macroprolactinomas [3] and 60–68% for giant prolactinomas [4, 5] (Table 1). This remission rate is not surprising as the mitotic rate and proliferation index of the giant invasive tumors is only mildly increased relative to the smaller macroprolactinomas [20]. Maiter and Delgrange [5] summarized 13 series including a total of 97 patients with giant prolactinomas primarily treated with bromocriptine or cabergoline. Prolactin normalized in 58 patients (60%) and was significantly suppressed in most of the remainder. After a mean follow-up of 37 months, considerable tumor shrinkage (30% reduction in tumor diameter or 65% decrease in adenoma volume) was observed in 74% of patients, and visual improvement was observed in 96% of the patients who presented with visual field defects. Half of all male patients with giant prolactinomas have persistent hypogonadism while on dopamine agonists. In a large series from Mexico of 42 men with giant prolactinomas [21], cabergoline treatment (median dose, 2 mg/week) resulted in prolactin normalization in 68% and reduction of >50% of tumor volume in 87%. Recovery of hypogonadism and visual improvement occurred in 32 and 68%, respectively. Only 6 men required surgery. In another cohort of 18 patients with particularly large giant macroprolactinomas measuring >60 mm in diameter [7], which are typically characterized by aggressive behavior and invasiveness with massive extrasellar extension, the authors reported a similar remission rate to the Mexican

study (61%) using a high dose of cabergoline (median dose, 3.5 mg/week) for a median of 20 months. However, testosterone normalized in only 6 of the 16 male patients [7] and 9 patients (50%) required surgery (Table 1). Only 10% of all giant prolactinomas occur in women [6] at a median age of 44 years at diagnosis. One study of 34 women with giant prolactinomas showed that cabergoline treatment effectively normalized prolactin levels in 55% [6].

Cabergoline is the preferred dopamine agonist over bromocriptine for the treatment of giant prolactinomas because it has a better effect on prolactin levels, albeit with no advantage in terms of tumor shrinkage [22]. In patients with bromocriptine-resistant giant prolactinomas, prolactin levels may normalize when treatment is switched to cabergoline [23]. The treatment protocol with cabergoline consists of the same starting dose as for macroprolactinomas (0.5–1.0 mg/week), which is then individually adjusted according to the prolactin response. Rapid dose escalation may lead to massive tumor shrinkage with a potential risk of apoplexy or CSF leak [24, 25]. Lifetime continuous dopamine agonist treatment is required in almost all patients to maintain prolactin suppression and prevent tumor regrowth. Withdrawal of treatment poses a risk of rapid tumor re-expansion, but a dose decrease is possible if long-lasting normoprolactinemia is preserved and the tumor mass is controlled.

Pituitary Surgery

Transsphenoidal or transcranial resection may be offered to the subset of patients with giant prolactinoma for whom even high-dose medical therapy fails to achieve tumor and hormonal control [26], and patients with apoplexy or complications of pharmacological treatment (CSF leak). The reported rate of surgery following first-line dopamine agonist treatment is 13–14% [5]. Severe chiasmal compression might also lead to a decision to operate, although even severe optic damage and significant visual field defects can improve with medical treatment alone [4, 5].

However, surgery is rarely curative. Most patients will not achieve hormonal remission postoperatively [3, 5], will remain with a significant adenoma residue, and will require continuous medical treatment. Surgical resection may also be hampered by intratumoral fibrosis, which may develop following long-term dopamine agonist management [27, 28]. Moreover, surgery in patients with gigantic tumors can be associated with complications

such as diabetes insipidus, mental deterioration, CSF leak, meningitis, worsening vision, and even perioperative mortality [19].

Radiotherapy

Radiotherapy may serve as adjuvant therapy in patients with giant prolactinoma resistant to dopamine agonists, preferentially after debulking surgery. To increase the chance of success, discontinuation of dopamine agonist treatment before and during radiotherapy is frequently recommended. It is difficult to distinguish the effects of radiotherapy from the effects of concurrent medical treatment or previous surgery. In a series of 20 patients with invasive giant prolactinomas treated with bromocriptine, 11 underwent also adjuvant radiotherapy. The authors concluded that traditional radiotherapy did not enhance the effect of bromocriptine on tumor shrinkage compared to patients who did not receive radiotherapy [29]. Irradiated patients should be followed regularly for the possible development of pituitary hormone dysfunction.

Other Treatment Options

Temozolomide

Temozolomide (TMZ) is an oral alkylating agent used in the treatment of malignant brain tumors. It was introduced in 2006 for the treatment of aggressive pituitary adenomas and carcinomas, with good results [30, 31], and in the last decade, studies have found it to be a useful option for certain aggressive and resistant giant and malignant prolactinomas. TMZ is generally well tolerated, but some patients experience nausea, fatigue, leukopenia, and thrombopenia. A recent systematic review of the literature [32] yielded 23 cases of prolactin-secreting adenomas and 19 of prolactin-secreting carcinomas treated with TMZ. The tumor decreased to varying extents in 76% of patients, with a significant reduction of prolactin level in 75%, including a few patients with prolactin normalization. However, researchers tend to report rare tumors with a good response to novel therapies rather than resistant ones, leading to a possible publication bias. Some studies of aggressive pituitary adenomas reported a strong association between negative staining for the DNA repair protein O⁶-methylguanine-DNA methyltransferase (MGMT) and good response to TMZ [33].

Testosterone Replacement

Persistent hypogonadism is very common in patients treated with dopamine agonists, even after normoprolactinemia is achieved. This finding is attributed to the long-standing mass effect of the giant tumor, with continuous destruction of the normal pituitary gonadotrophic cells, precluding gonadotropin stimulation of testosterone. Apart from sexual dysfunction and suppressed libido, hypogonadism in men may be associated with reversible anemia [34] and osteoporosis. In these cases, testosterone replacement is usually beneficial. There is a potential risk of tumor enlargement due to testosterone aromatization to estradiol, with a possible direct effect of estradiol on lactotroph cell hyperplasia, but it occurs only rarely [35].

Treatment Complications

Besides CSF leak/rhinorrhea discussed above [25], long-term use of dopamine agonists may be associated with several other rare complications. Fibrosis of cardiac valves leading to cardiac valvulopathy was demonstrated in patients with Parkinson's disease treated with high doses of dopamine agonists. However, at the doses typically used for prolactinomas, cabergoline appears to be safe, with no evidence of a clinically relevant effect on cardiac valve function [36]. Impulse control disorders have been reported in patients receiving dopamine agonists for prolactinoma, including disruptive hypersexuality ("Dopa-testotoxicosis") [37], financial loss, and reduced work performance. Usually, these phenomena were reversed on dose decrease or discontinuation of the drug.

Conclusion

Giant prolactinomas are generally benign but they may be aggressive and invasive, disrupting nearby structures and increasing prolactin levels. They show a fairly good response to medical treatment with dopamine agonists, combined with surgery in some patients and radiotherapy if required. This multimodal approach may effectively suppress prolactin levels to normal or close to normal in most cases, often accompanied by dramatic tumor shrinkage. The clinical response rate is almost similar to that reported for smaller medically treated macroprolactinomas.

Statement of Ethics

The author has no ethical conflicts of interest to disclose.

Disclosure Statement

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