CLINICAL STUDY

Effectiveness of long-term cabergoline treatment for giant prolactinoma: study of 12 men

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Abstract

Objective: To review our experience with cabergoline, a D2-selective dopamine agonist, for the treatment of giant prolactinomas.

Design: A retrospective case series; descriptive statistics.

Methods: The study group included 12 men aged 24–52 years (mean 39.2 years) treated for giant prolactinoma at our centers from 1997 to 2006. Cabergoline was started at a dose of 0.5 mg/three times a week and progressively increased as necessary to up to 7 mg/week. Patients were followed by hormone measurements, sellar magnetic resonance imaging, and visual examinations.

Results: In ten patients, cabergoline served as first-line therapy. The other two patients had previously undergone transsphenoidal partial tumor resection because of visual deterioration. Mean serum prolactin level before treatment was $14\,393 \pm 14\,579$ ng/ml (range 2047–55 033 ng/ml; normal 5–17 ng/ml). Following treatment, levels normalized in ten men within 1–84 months (mean, 25.3 months) and decreased in the other two to 2–3 times of normal. Tumor diameter, which measured 40–70 mm at diagnosis, showed a mean maximal decrease of $47 \pm 21\%$; response was first noted about 6 months after the onset of treatment. Nine patients had visual field defects at diagnosis; vision returned to normal in three of them and improved in five. Testosterone levels, initially low in all patients, normalized in eight. There were no side effects of treatment.

Conclusion: Cabergoline therapy appears to be effective and safe in men with giant prolactinomas. These findings suggest that cabergoline should be the first-line therapy for aggressive prolactinomas, even in patients with visual field defects.

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Introduction

Prolactin (PRL)-secreting adenomas are the most common secreting pituitary tumors, accounting for approximately 40% of all pituitary adenomas. Microprolactinomas are more common than macroprolactinomas. In general, prolactinomas have a female predominance, and microadenomas occur more often in women, whereas macroadenomas are common in men.

Giant prolactinomas are a rare subset of macroadenomas, characterized by large size (more than 40 mm in diameter), high aggressiveness, and massive extrasellar involvement (1, 2). They are usually associated with very high serum PRL levels (> 1000 ng/ml).

Prompted by early reports of the benefits of bromocriptine in the management of hyperprolactinemia (3, 4), researchers have been successfully using different dopamine agonists for first-line treatment of prolactinomas (5, 6). Of these, cabergoline, a long-acting D2-selective dopamine agonist, has been found to

be highly effective in normalizing PRL levels and inducing shrinkage of micro- and macroprolactinomas in both men and women (7–12). Today, surgery is recommended for prolactinoma only in patients with an inadequate response to dopamine agonists (13).

The aim of the present study was to review our experience with long-term cabergoline treatment of giant prolactinomas.

Patients and methods

Patients

The study group consisted of 12 men with giant prolactinomas, who were diagnosed and treated at the Endocrine Institutes of Rabin Medical Center, and Sheba Medical Center, Israel between 1997 and 2006. All met the diagnostic criteria for giant prolactinomas, namely, tumor diameter over 40 mm, serum PRL level higher than 2000 ng/ml, and invasive

tumor growth pattern with mass effects. Tumor size was documented by the largest measurable diameter on magnetic resonance imaging (MRI) study performed before treatment.

Treatment protocol

The starting oral dose of cabergoline was 0.5 mg, administered twice in the first week and thereafter three times weekly. Doses were increased progressively every 2–3 months, as necessary, according to the degree of PRL suppression, until levels normalized and a decrease in dose could be safely considered. Serum testosterone level was measured in parallel with PRL. Sellar MRI was performed before treatment, 6 months after the onset of treatment, and then once yearly. Goldmann perimetry and clinical visual acuity examination were performed before treatment, 1–2 months after onset of treatment, and then every 3–6 months until findings normalized.

Hormone assays

Serum PRL levels were measured by immunometric assay (Immulite 2000; Diagnostic Products Corps. (DPC), Los Angeles, CA, USA), which has a sensitivity of 0.15 ng/ml. The intra-assay coefficients of variation (CV values) for PRL concentrations of 22 and 164 ng/ml were 2.3 and 3.8% respectively; the corresponding inter-assay CV values were 6%. Reference levels for men in our laboratory are 5–17 ng/ml. Levels greater than 200 ng/ml were calculated after appropriate serum dilutions. Total testosterone was determined by RIA (Coat-A-Count; DPC), which has a sensitivity of 0.1 ng/ml. The intra- and inter-assay CV values were 4 and 10% respectively. Reference levels for men aged 20–50 years are 3–10 ng/ml, and aged > 50 years, 1.8–8 ng/ml.

In addition, patients had thyroid function tests, cortisol, gonadotropins, growth hormone, and insulin-like growth factor-I measurements before and during treatment, using commercial kits.

Magnetic resonance imaging

Pituitary tumors were evaluated by 0.5 and 1.5 T MRI scanners in the sagittal, coronal, and axial planes before and after gadolinium administration. All tumor diameters were measured, and tumor shrinkage was evaluated as a reduction in maximal tumor diameter compared with baseline.

Statistical analysis

Results are expressed as mean ± s.d. Differences in patient- or tumor-related parameters by time to treatment response were calculated with Student's

unpaired *t*-test. A *P* value of <0.05 was considered significant.

Results

Age range of the study group was 24–52 years (mean 39.2 ± 10.3 years) at diagnosis (Table 1). Cabergoline served as the first-line treatment in ten patients. The other two patients (nos 1 and 3, Table 2) had previously undergone partial transsphenoidal resection of the pituitary tumor to urgently relieve visual deterioration. One received cabergoline immediately after surgery (patient 1), and the other (patient 3) was switched to cabergoline after 3 years on bromocriptine because of poor hormonal and tumor mass responses.

The dose of cabergoline was progressively increased from 1.5 to 2 mg/week in two patients, to 2.5 and 3 mg/week in one patient each, to 3.5 mg/week in four patients, and to 7 mg/week in two patients (median dose 3.5 mg/week); two patients continued with 1.5 mg/week with no dose increment. The drug was well tolerated by all patients, and in no case was it necessary to decrease the dose or discontinue therapy because of side effects.

At presentation, serum PRL level was extremely high in all patients, ranging from 2047 to 55 033 ng/ml (mean 14 393 ± 14 579 ng/ml). Seven patients presented with levels above 10 000 ng/ml (Table 2). PRL levels normalized in ten patients after 1–84 months of treatment (mean 25.3 months) and decreased to 2–3 times normal in two patients (treated with a weekly dose of 1.5 and 3 mg). One of the latter patients (no. 9) underwent transsphenoidal resection 1 year after cabergoline treatment, with no further effect on PRL level. Overall, PRL level decreased to a mean of 15 ± 10 ng/ml (99.8% suppression). Comparison of the patients by time to PRL response, i.e. normalization by 6 months (patients 4, 8, 9, 10, 12; Fig. 1a) or normalization, or near-normalization after 12 months (range 12–84 months; patients 1, 2, 3, 5, 6, 7, 11; Fig. 1b), revealed no significant differences between the groups in age, baseline PRL level, tumor size, or tumor shrinkage after treatment (Table 2). However, the late responders required a higher dose of cabergoline than the early responders (mean 4.3 vs 2.1 mg/week,

Table 1 Baseline characteristics of 12 men with giant prolactinomas.

Age at diagnosis (year)	39.2 ± 10.3
Range (year)	24–52
Basal prolactin level (ng/ml; normal 5–17)	14,393 ± 14,579
Range (ng/ml)	2,047–55,033
Adenoma diameter (max; mm)	47 ± 10
Visual field defects (n)	9
Basal testosterone (ng/ml; normal > 3)	1.2 ± 0.9
Previous tumor resection (n)	2

Table 2 Effects of cabergoline treatment in men with giant prolactinomas.

Pt. no.	Age (year)	Size (mm)	Visual fields		PRL (ng/ml)		Time to nadir (mo.)	Tumor shrinkage	TSS	Hypopituitarism	Dostinex (mg/week)
			Baseline	Treatment	Baseline	Nadir					
1	45	45×35	Bilateral	Left	11,406	38	30	Not observed	Before		3
2	31	40×40	Bilateral	Normal	2800	11	17	25,mm	Before		3.5
3	50	60	Bilateral	Bilateral	55,033	11	84	Empty sella	Before	Yes	3.5
4	24	70×60×55	Bilateral	Left	19,800	4	2	Sellar mass			3.5
5	34	40×40×30	Normal	Normal	2638	11	24	24,mm			3.5
6	41	60	Left	Normal	21,000	15	50	18,mm			7
7	24	40×30×35	Right	Improved	14,415	10	35	Sellar mass			2.5
8	31	50×45×50	Left	Normal	12,000	4	6	38,mm			2
9	49	40	Lt homony	Improved	5725	28	3	29,mm	On CAB	Yes	1.5
10	38	40×30	Normal	Normal	6051	10	1	NA			2
11	51	42	Right	Improved	2047	14	26	Mild shrinkage			7
12	52	40×30	Normal	Normal	19,800	20	5	20,mm			1.5

PRL, prolactin; TSS, transsphenoidal surgery; CAB, cabergoline.

Figure 1 Prolactin levels (ng/ml) after cabergoline initiation in men with giant prolactinomas. Prolactin is presented in a logarithmic scale. (a) Five early responders in whom serum prolactin levels normalized/near normalized in 6 months of treatment. (b) Seven late responders in whom serum prolactin levels decreased to normal or near-normal after 12 months of treatment or more.

$P < 0.05$). Both patients after transsphenoidal surgery were in the late responding group.

Baseline testosterone level was low (< 3 ng/ml) in all patients (mean 1.2 ± 0.9 ng/ml). Five patients also complained of erectile dysfunction or low libido. Testosterone normalized in eight patients (67%) after treatment; the mean for the whole group at the end of the study was 3 ± 1.7 ng/ml. Two of the four patients with persistently low testosterone levels also failed to achieve normal PRL levels.

Two patients (nos 3 and 9) had secondary hypoadrenalism and hypothyroidism that required hormone replacement.

Tumor size at diagnosis ranged from 40 to 70 mm (mean 47 ± 10 mm).

All tumors presented with suprasellar invasion and chiasmal compression, and almost all exhibited parasellar extension to the cavernous sinuses. In addition, we noted sphenoid sinus involvement in six patients, clivus extension in three patients, and mid-brain, third ventricle, frontal and temporal lobes, and cerebellar invasion in two patients each. In nine patients, a significant reduction in tumor volume was observed, usually evident 6–18 months after onset of treatment (Table 2, Fig. 2). One patient (no. 11) showed mild tumor shrinkage (Fig. 3) and one (no. 1) showed no change (Table 2). In the remaining patient (no. 10), tumor shrinkage could not be assessed because the MRI findings at treatment were unavailable. For the whole group, maximal diameter progressively decreased by a mean of $47 \pm 21\%$.

Figure 2 Large reduction in tumor mass depicted on gadolinium-enhanced MRI scan (left, coronal; right, sagittal) in two patients after (a) 17 months (patient 7) and (b) 50 months (patient 6) of cabergoline treatment.

Nine patients had visual field defects at presentation; bilateral in five and unilateral in four (Table 2). The visual fields normalized in three of them within 1–3 months of treatment, and significantly improved in five (Table 2). One patient (no. 3) showed no change. This patient underwent transsphenoidal surgery before medical treatment and his PRL level normalized only after 84 months, with massive tumor shrinkage.

Discussion

Giant prolactinomas are rare invasive large pituitary tumors, usually identified in men (1, 2). Surgical debulking may be employed to induce rapid optic decompression and visual improvement, or to prevent pituitary apoplexy in patients refractory to dopamine agonists (14). However, complete surgical removal of giant tumors that extend into the suprasellar,

Figure 3 Mild prolactinoma shrinkage on MRI after 37 months of cabergoline treatment in patient (no. 11) with normalized prolactin levels.

parasellar, and infrasellar areas is difficult, and biochemical cure is rare even after extensive tumor removal (15–17). After surgery, most patients still require medical therapy (1, 15, 16), as occurred in two of our patients as well. Moreover, surgery for giant pituitary adenomas is associated with high mortality and morbidity rates, especially when done through craniotomy (18, 19). These series (18, 19) reported 11 operative deaths out of 93 operated patients, and increased morbidity, including diabetes insipidus, mental deterioration, visual loss, and cerebrospinal fluid leaks.

The present study describes the outcome of 12 men with giant aggressive PRL-secreting tumors treated with cabergoline, a D2-selective dopamine agonist, widely used to treat prolactinomas. In ten of them, cabergoline was the first-line therapy. PRL levels were successfully suppressed to normal in ten patients (83%). Significant tumor shrinkage was noted in 90% of patients and visual improvement in 89%. In previous series of men with non-giant macroprolactinomas treated with cabergoline (10, 11), the rate of PRL normalization was approximately

75%. However, the median dose of 1–1.5 mg/week was much lower than the 3.5 mg/week in our patients.

In a recent review of seven series of a total of 49 patients with giant prolactinomas treated with bromocriptine ($n=35$) or cabergoline ($n=14$), Gillam *et al.* (13) reported a 65% rate of PRL normalization. Saeki *et al.* (20) found bromocriptine therapy (5–15 mg/day) effective in controlling PRL levels in six out of ten patients with giant prolactinomas, and Shrivastava *et al.* (1), who treated ten men with bromocriptine (10 mg/day), noted PRL suppression to normal in two cases, and a dramatic reduction to 30–100 ng/ml (99.9% suppression) in the remainder. In two series of a total of 14 subjects (Table 3) treated by cabergoline (1.5–10.5 mg/week; median dose 2.25 mg/week), PRL level normalized in eight and dropped to approximately 96–98% of baseline in most of the remainder (2, 21).

In the present series, which is the largest to date addressing long-term cabergoline treatment of giant prolactinomas, PRL was suppressed to normal or near-normal levels in all cases, representing a better response

Table 3 Effectiveness of cabergoline treatment in three series of patients with giant prolactinomas.

	Shimon <i>et al.</i> current study	Corseello <i>et al.</i> (2003) (Ref. (2))	Minniti <i>et al.</i> (2002) (Ref. (21))
No., gender	12 men	10 men	4 men
Mean age (year)	39.2	48.8	48.2
Mean basal prolactin (ng/ml); range	14 393; 2047–55 033	5794; 1230–22 916	2212; 660–6500
Mean maximal diameter (mm)	47	41	Destructive skull base tumors
Previous surgery	2	4	1
Mean cabergoline dose (mg/week)	3.4	3.3	1.6
Prolactin normalization	10/12	5/10	3/4
Visual defects improvement	8/9	6/7	1/1
Significant tumor shrinkage	9/11	9/10	1/4

rate than previously reported. Moreover, testosterone levels normalized after treatment in 67% of the patients, and some reported an improvement of libido and potency. Interestingly, the time to the drop in PRL from the onset of treatment ranged from several months to more than 2 years. This variation was not explained by tumor size or baseline PRL level, and it was not correlated with tumor shrinkage. We assume it reflects different degrees of sensitivity to cabergoline, probably related to the level of D2 dopamine receptor expression in the prolactin-secreting tumors, the ratio of the two receptor isoforms, or the activity of Gi/Go proteins coupled to adenylate cyclase in lactotroph cells (22, 23).

Cabergoline dose was progressively increased from 1.5 mg/week to the individually effective dose at an interval of not less than 2–3 months. This relatively slow rate of dose escalation was used to prevent potential adverse effects (see below). However, the dose can probably be increased more rapidly. By contrast to the PRL normalization time of months to years and the 1-year or more interval to tumor shrinkage, the effect of cabergoline treatment on visual acuity and visual fields was apparent already after days or weeks. This finding is supported by other studies as well, and reinforces the effectiveness of cabergoline treatment. Gonadal dysfunction was reversed in 67% of our patients upon normalization of hyperprolactinemia. Moreover, only two men in our series had secondary hypoadrenalism and hypothyroidism. This emphasizes the potential reversibility of pituitary function in patients harboring invasive and aggressive prolactin-secreting pituitary tumors, usually recovering without developing hypopituitarism. This also supports the use of medical treatment over surgery for giant prolactinomas.

Complications of medical treatment with high-dose dopamine agonists for large invasive prolactinomas are uncommon. They may include cerebrospinal fluid leakage (24), chiasmal herniation, and pituitary apoplexy, none of which developed in our series, despite the high dose of cabergoline used in some of the patients. Some doses used are beyond those recommended in the package insert, but large doses are sometimes needed for certain patients with large tumors. The dose can be safely increased as long as the patient tolerates it without adverse effects. In Parkinson's disease, far larger doses of cabergoline are used, approximately 4 mg/day, and sometimes up to 20 mg/day, and these doses are usually well tolerated (25). Recently, the association between mitral valve insufficiency and high-dose cabergoline prescribed for Parkinson's disease was reported (26). Thus, patients using high-dose cabergoline should be monitored by echocardiography for this rare adverse effect.

In summary, the present study demonstrates that cabergoline is as safe and effective for the treatment of giant prolactinomas as for smaller macroprolactinomas in men, even when administered over a long term in relatively high doses. We recommend that pharmacologic agents, and not pituitary surgery, should be the

first-line treatment for aggressive prolactinomas, even in the presence of visual defects.

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