

ABSTRACT

Background: Treatment of invasive prolactinoma, which has several characteristics including invasive growth into cavernous sinuses and formation of giant adenomas compressing adjacent neural structures, resulting in neurological dysfunction, has been very challenging. There are relatively few reports available describing long-term treatment outcome.

Aims of the study: In this study we evaluate the results of cabergoline administration as initial treatment during 4 years follow up period.

Methods: We prospectively categorized 36 patients into four groups according to the results of 3 months of cabergoline treatment: group 1, tumor volume reduction (TVR) >25% with normalized serum prolactin (NP) (n = 24); group 2, TVR>25% without NP (n = 4); group 3, TVR <25% with NP (n = 5); and group 4, TVR <25% without NP (n = 3).

Results: During follow-up, 22 patients (91.7%) in group 1 achieved TVR>50% with NP. Three patients (75%) in group 2 achieved TVR>50% with NP after treatment for 8 months. In group 3, four patients (80.0%) continued medication because of improvement of symptoms and achieved additional TVR(18.8–46.4%). Surgery was performed on five patients (one in group 2, one in group 3,

and three in group 4), and complete resection was achieved in four (80.0%). Overall, 25 (69.4%) of the 36 patients treated with cabergoline had complete response and 6 (16.7%) had partial response but did not require surgery. Thus, the overall response rate was 86%, with only five patients (14%) requiring surgical debulking. NP was not achieved by surgery alone in all cases, even after total resection of tumor.

Conclusion: Patients who achieve TVR>25% with NP with 3 months of cabergoline administration had a high possibility of showing good long term response (TVR>50% with NP) to cabergoline. A higher dose of dopamine agonist (DA) should be considered for patients who achieve TVR>25% without NP.

Keywords: Cabergoline , Dopamine agonist , Invasive prolactinoma, Pituitary adenoma

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INTRODUCTION

Prolactinoma is the most common type of functional pituitary tumor. It accounts for approximately 25–40% of pituitary tumors and up to 60% of functioning ones. ^(1,2,3)

For most patients with prolactinoma, dopamine agonists (DAs) have been regarded as the choice for initial treatment. ^(4,5,6,7,8,9,10)

DAs have been effective in reducing tumor volume and lowering serum prolactin levels (PRLs) in prolactinoma, whether it is located in the intrasellar or extrasellar space. However, the treatment of invasive prolactinoma, which has several characteristics including

invasive growth into cavernous sinuses and formation of giant adenomas compressing adjacent neural structures, resulting in neurological dysfunction, has been very challenging. Although transsphenoidal microsurgery has been applied in many cases of invasive pituitary tumors, the possibility of surgical cure is nearly nonexistent, especially for invasive prolactinomas.

Therapeutic modalities using DAs alone or in combination with surgery or radiation have been applied. ^(6, 7, 11,12,13) Among various drugs for prolactinomas,

bromocriptine has been regarded as a first-line agent for invasive prolactinoma^(14,15,16,17), and continuous administration of bromocriptine is mandatory even if the tumor shrinks and an elevated PRL level falls. Compared with bromocriptine, cabergoline is a newly introduced drug for hyperprolactinemia treatment in our country in the last decade. Cabergoline was more effective in reducing PRL and tumor volume, and some reports found that side-effects occurred three times more frequently with bromocriptine than with cabergoline.⁽¹⁸⁾ Moreover, several studies have shown that cabergoline is an effective alternative for about 80% of cases of bromocriptine-resistant macroprolactinoma.⁽¹⁷⁾ In this study, we evaluate the results of cabergoline administration as initial

treatment for 36 patients with invasive prolactinoma during an average of 4 years of follow-up. We also analyze final treatment results as compared with the 3-month initial response to cabergoline according to tumor volume reduction (TVR) and serum prolactin level.

METHODS

We conducted a study of cabergoline treatment as primary treatment for 36 cases of invasive prolactinoma at between February 2007 and December 2018 in The Neurosciences Hospital, Baghdad/Iraq. Mean patient age was 42.5 years (males, 44.2 years; females, 37.8 years), and follow-up period was 4 years. Symptoms are summarized in table 1.

Table 1 Clinical manifestations in 36 patients with invasive prolactinomas

Symptom and sign	Female (n = 11)	Male (n = 25)
Visual field defect	3 (27.3%)	19 (76%)
Sexual dysfunction (decreased libido, impotence)	1 (9.1%)	14 (56%)
Amenorrhea (female), infertility	9 (81.8%)	2 (8%)
Headache and dizziness	3 (27.3%)	9 (36%)
Ocular movement abnormality (3rd, 4th, 6th cranial nerve palsy)	2 (18.2%)	0 (0%)
Galactorrhea	8 (72.7%)	0 (0%)

Eighty-two percent of female patients complained of amenorrhea and/or infertility, and 76% of male patients had visual field defects. More than 50% of male patients had sexual dysfunction, including decreased libido and impotence. We evaluated the patients using careful history-taking, physical examination, and basal pituitary hormone assay (including PRL). Changes of pituitary hormone levels after cabergoline treatment were analyzed by paired t-test or Wilcoxon signed-rank test as appropriate. Subsequently, magnetic resonance imaging (MRI) scans of the sella area were obtained. Invasive prolactinoma was defined as (1) PRL greater than 150 ng/ml, (2) invasion of the

cavernous sinus corresponding to grade III or IV according to the classification of Knosp et al.⁽¹⁹⁾, and (3) clinical symptoms of hyperprolactinemia and a mass effect.

Treatment and follow-up protocol

Once invasive prolactinoma was clinically diagnosed, cabergoline treatment was started at low dose in all cases (0.5 mg/week cabergoline at bedtime), and the dosage was gradually increased to 0.5 mg/day within 2–4 weeks. The maximum dose was maintained for 3 months to ensure a sufficient period for the drug effect even though PRLs fell below normal range. Three months after medication was started, tumor volume was

measured again using MRI, and we checked response to treatment by evaluating TVR and PRLs. We prospectively categorized all patients into four groups according to early response to cabergoline by evaluating TVR and normalization of serum prolactin (NP) level after 3 months of cabergoline administration: group 1, TVR >25% with NP (n = 24); group 2, TVR >25% without NP (n = 4); group 3, TVR <25% with NP (n = 5); and group 4, TVR <25% without NP (n = 3). PRLs were measured every 3 months. Follow-up MRIs were performed at 3 and 6 months, then annually thereafter. Cabergoline dosage was reduced to 0.25 mg/day after confirming considerable tumor reduction, sustained NP, and clinical improvement.

RESULTS

Group 1 (TVR>25% with NP, n = 24)

During the initial 3 months of medication, visual symptoms (15/24, 62.5%) immediately improved in all patients (100%). Sexual dysfunction (11/18, 61%) improved in three male patients within 3 months, and in nine male patients after 3 months of medication. Menstruation resumed in three (50%) out of six female patients (100%) who complained of amenorrhea during the initial 3-month treatment. The remaining three patients also restarted menstruation after 3 months of medication. After 3 months, the average TVR of the 24 patients was 58.2% (range 27.9–100%). More than 50% TVR was achieved in 18 patients (75%, good responders). All 24 patients continued the medication, and 22 out of 24 patients (91.7%) achieved more than 50% TVR during the 4 years follow-up period. Two patients showed less than 50% TVR (31.7% and 43.7%, respectively) for over the 4 years follow-up period.

Group 2 (TVR>25% without NP, n = 4)

Symptoms, including headache and gonadal dysfunction, were improved between 1 week and 3 months after initiation of medication. Visual field defects also improved with only cabergoline administration in all patients (100%). The average TVR reduction was 53% (range 34–100%) at 3 months. Although complete NP was not achieved, three patients showed more than 80% reduction of PRLs. Cabergoline was continued for these three patients. Their PRLs were normalized with continuous medication at 5–9 months of medication, and the final TVR was 87.5% (range 77.7–100%). These three patients were categorized as the cabergoline responsive group. One of these patients showed tumor re-growth after 4 years follow-up; therefore, radiosurgery combined with cabergoline was applied; TVR to 77.7% at 1 year after initiation of radiosurgery and cabergoline treatment was achieved. The PRL of one patient did not show any change (>300 ng/ml) after 3 additional months of cabergoline treatment, although TVR was 56%; therefore, we proceeded with transsphenoidal resection and performed near-total removal of the tumor. This patient achieved NP under cabergoline treatment after surgery.

Group 3 (TVR<25% with NP, n = 5)

In this group, initial mean TVR was only 9.1% (range 0–22%), although all patients showed NP after 3 months of cabergoline treatment. Surgery was recommended for one patient who recorded initial prolactin level of 166.6 ng/ml and showed hypopituitarism [thyroid-stimulating hormone (TSH) and gonadotropin deficiency] to rule out nonfunctioning pituitary tumor, applying transsphenoidal removal of the tumor. Four patients achieved NP, and visual field defects were improved in all. They maintained the maximum cabergoline dosage for 6 months, and their gonadal symptoms were

recovered afterward. Although additional TVR was achieved, it was less than 50% (mean 28.7%, range 18.8–46.4%). Visual disturbance and ptosis improved dramatically in 1 week for one patient, and gonadal dysfunction was partially improved later. Final TVR of this patient was 46.4%. This patient can be categorized as partially responsive to cabergoline.

Group 4 (TVR<25% without NP, n = 3)

Three patients achieved neither TVR >25% nor NP 3 months after the initial cabergoline trial. They underwent surgical resection of the tumor, finally. One patient persisted with a visual field defect after 3 months of cabergoline treatment, refused surgery at the first recommendation, and continued medication for another 4 months. He eventually underwent transsphenoidal resection after 7 months of cabergoline treatment, and only partial removal of the tumor was possible due to severe peritumoral fibrosis. His visual field defect improved after surgery. His PRL was still more than 300 ng/ml, and his TVR was only 26% at last follow-up, despite surgical removal with concomitant administration of cabergoline. He refused all further treatment except cabergoline treatment, including radiation therapy.

One patient underwent surgery because of increasing serum prolactin level (630 to 1132 ng/ml) and persistent eye pain during medical treatment. She had tumor regrowth and hyperprolactinemia that persisted despite postoperative cabergoline treatment. Therefore, adjunctive radiosurgery was performed 3.5 years after surgery. Regular menstruation and NP were achieved with cabergoline treatment 8 months after radiosurgery.

Regarding changes of other pituitary hormone levels besides prolactin level during medical treatment (average 34.5 months) without regard to the four groups, free T4 level increased after cabergoline treatment from 0.86 ± 0.06 to 1.03 ± 0.05

ng/dl ($p = 0.035$). Total testosterone level in male patients also increased from 165.05 ± 27.43 to 364.32 ± 40.11 ng/dl ($p = 0.001$). Other hormone levels, including growth hormone (GH), leutinizing hormone (LH), follicle-stimulating hormone (FSH), TSH, and cortisol level, did not show any significant changes before and after cabergoline treatment.

DISCUSSION

We have described the clinical outcomes in patients with invasive prolactinoma by analyzing the final and initial 3-month results of cabergoline therapy for 36 cases of invasive prolactinoma. The complete response rate (TVR >50% with NP) of cabergoline treatment was 70% (total 25/36; group 1: n = 22, group 2: n = 3), showing that medical treatment with cabergoline was very effective in most patients with invasive prolactinoma, which is the current primary recommendation for initial therapy as proven before in micro- and macroprolactinomas. The remaining 11 patients who did not achieve TVR >50% with NP (responsiveness) after cabergoline treatment could be categorized as dopamine resistant. However, all invasive prolactinomas with dopamine resistance did not have to be treated surgically to achieve TVR >50% with NP. Only five patients underwent surgical treatment due to increasing PRL or no improvement of visual field (V/F) defect despite medical treatment. Though the remaining six patients were considered to be dopamine resistant, they showed partial response and subsequent improvement of symptoms, such as sexual dysfunction.

In summary, 25 (69.4%) of the 36 patients treated with cabergoline had complete response and 6 (16.7%) had partial response but did not require surgery. Thus, the overall response rate was 86%, with only five patients (14%) requiring surgical debulking. There is some discrepancy between reduction of tumor volume and

serum prolactin level in response to cabergoline. Therefore, we prospectively categorized into four groups, combining these two response factors to initial cabergoline treatment, and observed the final results in each group. The average TVR was 58.2% in group 1 patients who responded well to cabergoline, and 18 patients showed over 50% TVR on MRI 3 months after treatment. After continuous administration of cabergoline, 22 of 24 patients (92%) in group 1 achieved more than 50% TVR. Therefore, patients who achieve TVR>25% with NP with 3 months of cabergoline administration have a high likelihood of showing good long-term responsiveness (TVR >50% with NP) to cabergoline. In addition, it is necessary to keep in mind that rapid TVR while taking cabergoline in invasive prolactinomas sensitive to dopamine agonist such as those in this group 1 can precipitate development of cerebrospinal fluid leak, which may require timely surgical intervention.^(16, 18, 20)

In group 2 (TVR >25% without NP), three patients maintained cabergoline treatment because they showed remarkable level of PRL reduction as compared with initial levels and their clinical symptoms were also markedly improved. These patients achieved NP with continuous medication for 5–9 months. Therefore, after 3 months, a higher dose of DA should be considered for patients who achieve TVR>25% and significant decrease of PRL. These patients may be delayed responders. Although all four patients in group 2 initially showed remarkable reduction of tumor volume, a longer period of cabergoline administration was required for three patients, and surgery with adjunctive DA treatment was needed for one patient to achieve NP. Among the four patients, three had larger tumor volumes in contrast to the median volume of group 1 patients, especially two patients in whom the tumor volume was 2–5 times larger

than those of group 1 patients. This suggests that a large tumor requires a longer period of medication, and also that surgical removal of tumor mass would be necessary for NP. In addition, maintaining the maximum tolerable dosage until the follow-up MRI was also important. If follow-up MRI showed less than 25% reduction of tumor mass, the possibility of insufficient dosage of cabergoline should be considered. Two patients in our study had received prior cabergoline treatment for several months before visiting our hospital, and MRI showed no significant TVR from this medication. Higher dosages of cabergoline for these two patients successfully induced TVR. This indicates that the maximum tolerable dose should be started from the beginning of treatment. In two patients, initial prolactin level was not high (200, 171 ng/ml) although they had large and invasive tumors. Diluted PRL turned out to be over 2,000 ng/ml, displaying the so-called “hook effect.” The hook effect is limited to large tumors. In one report, the mean tumor diameter was 51 mm.^(21,22) Because this effect has been reported to occur in as many as 6–14% of patients with pituitary macroadenomas, it is advisable to dilute the serum specimen for prolactin assays in all patients with pituitary tumors larger than 3 cm. For group 3 (NP without TVR>25%), additional use of DA did not induce TVR >50%; therefore, dopamine resistance was suspected. Pharmacological resistance to DA is defined as failure of NP and TVR<50%.^(6, 23, 24) The amount of resistance to cabergoline was small in group 1 (8.3%). However one patient in group 2, who showed TVR >25% at 3 months, later developed resistance. In group 3, all who were maintained with cabergoline continuously showed resistance. These findings indicate that, in group 2 patients, the DA resistance rate can increase and the decision for surgical treatment should be made, especially in

patients with visual symptoms or cranial nerve palsy, at the end of a 3-month trial of DA. After comparing the outcome between groups 2 and 3, we found that TVR as early response to cabergoline is a more reliable indicator than NP in predicting long-term response to cabergoline. Determining the timing of surgery has become important, because prolonged use of DAs has been known to induce peritumoral fibrosis, which makes it more difficult to remove the tumor and increases the risk of surgical complications. Although the duration and dosage of medication, and the appropriate timing of surgery for patients who are resistant to dopamine agonists have been studied, controversy remains.^(12, 16, 18, 24, 25) In one patient in group 4, surgery was delayed until 7 months of medication because he refused the operation. Only partial decompression was possible because of severe peritumoral fibrosis. This had also been indicated in previous reports of treatment with cabergoline of longer than 3 months, where it was difficult to remove the entire tumor because of peritumoral fibrosis.^(11,26,27) In another report⁽¹⁵⁾, 6 weeks of DA treatment was suggested to reduce the risk of secondary neurological sequelae after surgery. Our data suggests that the initial cabergoline trial period should be 3 months to avoid difficulty in surgery because of peritumoral fibrosis. In the immunohistochemical staining of five surgically removed tumor tissues, two were revealed to be prolactin negative tumors, although PRLs were higher than 150 ng/ml. This suggests that a higher prolactin level does not always provide diagnostic value for prolactinoma. In one patient in group 3, initial serum prolactin level was 167 ng/ml, the lowest level in this study. After administering cabergoline for 3 months, the serum prolactin level was normalized to 2.3 ng/ml, but tumor size was reduced by only 15%. A

prolactinoma diagnosis is most likely to be made when serum prolactin levels are greater than 200 ng/ml. However, if there is a pituitary mass lesion with serum prolactin levels lower than 200 ng/ml, nonfunctioning pituitary adenoma (NFPA), which may also compress the pituitary stalk and cause hyperprolactinemia, should be included in the differential diagnosis.⁽²⁸⁾ It is often difficult to differentiate prolactinoma from hyperprolactinemic NFPA, particularly in patients with pituitary macroadenoma, as in this patient. When macroadenoma with serum prolactin levels lower than 200 ng/ml is found, DA treatment is considered first. Although serum prolactin levels can be lowered by DA treatment in patients with NFPA, tumor size is not reduced in the majority of patients.⁽²⁹⁾ In the case of this patient, surgery was performed upon suspicion of NFPA. Immunohistochemical study of the excised tumor specimen revealed ACTH immunoreactivity.

CONCLUSION

Cabergoline was very effective in 70% of patients with invasive prolactinoma. Patients who achieve TVR>25% and NP with 3 months of cabergoline administration have a high possibility of showing good long-term responsiveness (TVR>50% with NP) to cabergoline. A higher dose of DA should be considered for patients who achieved TVR>25% and/or significant decrease of PRL. Initial TVR >25% is more predictive than serum prolactin level for successful long term results of cabergoline treatment for invasive prolactinoma.

Surgical treatments were performed on those patients showing unresponsiveness, such as persistent visual field defects, despite medical treatment. However, NP was not achieved by surgery alone in all cases, even after total resection of tumor.

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