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Effectiveness of Cabergoline in Reduction of Tumor Volume and Suppression of Prolactin in Treatment-Naive Prolactinomas and the Correlation of T2-weighted Signal Characteristics of Adenomas with Their Response to Treatment

ABSTRACT

Objective: Cabergoline is a potent dopamine receptor agonist commonly used in the treatment of hyperprolactinemia. However, there are scarce data on the imaging characteristics of prolactinomas that could predict the response to treatment. The present study prospectively evaluated the effectiveness of cabergoline in the reduction of tumor volume and serum prolactin levels in treatment-naive cases of prolactinomas besides evaluating the imaging features of tumors on T2-weighted magnetic resonance imaging that could potentially predict the response to treatment.

Methods: The present study evaluated 83 prolactinomas (52 micro- and 31 macroprolactinomas) for a 24-month period. The T2-weighted signal characteristics of prolactinomas were evaluated at the start of treatment in addition to the estimation of tumor volumes and prolactin levels. T2-weighted signal characteristics of tumors allowed the categorization of tumors into homogeneous and heterogeneous groups. Patients were started on cabergoline therapy, and thereafter, serial magnetic resonance imagings were performed at 4-, 8-, 12-, 18-, and 24-month intervals to monitor the changes in tumor volume and prolactin levels.

Results: A total of 30 (27 micro- and 3 macroadenomas) patients showed complete disappearance of tumor at 24 months. More than a 75% reduction in tumor volume was noted in 82.7% of microadenomas and 78.6% of macroadenomas. More than a 75% reduction in prolactin levels was seen in 88.5% of microadenomas and 77.9% of macroadenomas at 24 months. After 1 year of treatment with cabergoline, 68.6% (35/51) showed normalization of prolactin levels and 64.7% (33/51) showed more than 50% reduction in tumor volume in the homogeneous group. In comparison, only 28.12% (9/32) showed normalization of prolactin levels and 31.25% (11/32) showed >50% tumor volume reduction among the heterogeneous group. Heterogeneous prolactinomas had more number of macroadenomas and were significantly larger and more secreting compared to homogeneous tumors at baseline (all $P < .05$)

Conclusion: Cabergoline administered for 12-24 months induced a significant tumor volume reduction with amelioration of clinical symptoms of prolactin excess and normalization of serum prolactin levels. T2-weighted homogeneous tumors had a more favorable outcome in comparison to the heterogeneous tumors.

Keywords: Cabergoline, MRI, prolactin suppression, prolactinomas, tumor shrinkage

Introduction

Prolactin-secreting tumors account for 30%-40% of pituitary adenomas and represent the commonest functional neoplasms of the pituitary gland.[1] Prolactinomas are categorized into 2 subgroups based on size. Tumors with a size of less than 10 mm are referred to as microprolactinomas, whereas tumors with a size of 10 mm or more are called as macroprolactinomas.[2]

Patients with prolactinoma present with a broad repertoire of clinical symptoms evolving principally from hyperprolactinemia-induced suppression of the gonadotroph axis. Females usually present with galactorrhea, amenorrhea, or infertility, whereas men present with erectile dysfunction and reduced libido. Additionally, large tumors may press upon the surrounding structures and produce visual disturbances due to optic chiasm compression or hypopituitarism due to the compression of the adjacent pituitary parenchyma.[2,3]

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Generally, all symptomatic prolactinomas warrant treatment. However, galactorrhea, infertility, hypogonadism, and mass effect due to tumors constitute specific indications for treatment.[4] Dopamine agonists (DA) are the preferred first-line drugs for the treatment of prolactinomas.[5-8] Among the several available DA agonists, cabergoline (CAB) and bromocriptine (BRC) are commonly used.[9,10] Owing to the higher reported rates of normoprolactinemia, a convenient once or twice weekly dosage of CAB is used more often compared to BRC.[11-14]

Magnetic resonance imaging (MRI) is the diagnostic modality of choice for the detection of pituitary adenomas and the estimation of their size.

Emerging data suggest that T2-weighted (T2W) signal characteristics of growth hormone-secreting pituitary tumors can predict the response to somatostatin analogs. It has been reported that somatotropinomas that exhibit T2W hypointense signal intensity are usually smaller in size, less invasive, and more responsive to treatment.[15,16] Whether the baseline imaging characteristics of prolactinomas can predict response to treatment remains largely unexplored. There are scarce data on baseline T2W imaging characteristics of prolactinomas vis-a-vis their response to pharmacological treatment.[17,18]

The present study aimed to evaluate the effectiveness of CAB in the reduction of tumor size and the suppression of prolactin levels in newly detected cases of pituitary adenomas. The present study also aimed to explore if pre-treatment T2W signal characteristics of prolactinomas can predict the response to treatment.

Material and Methods

Study Design and Patient Cohort

This was a prospective single-center study covering a 2-year study period from October 2018 to October 2020. The study was approved by the Institutional Ethical Committee of our institution, and informed consent was obtained from all patients. The study did not require any funding, and nominal fees required for investigations was paid by the patients. Symptomatic patients with biochemical evidence of hyperprolactinemia and imaging evidence of pituitary adenomas were recruited for the study. All participants were examined by 1.5-Tesla superconducting magnetic resonance imager (Magnetom Avanto, Siemens Medical System, Erlangen, Germany) with a standard head coil. After the preliminary localizing sequence, the imaging protocol included axial fluid-attenuated inversion recovery sequence, sagittal T1-weighted (T1W) spin-echo sequence, coronal T1W spin-echo sequence, sagittal T2W turbo spin-echo sequence, coronal T2W turbo spin-echo sequence followed by dynamic post-contrast acquisition performed after injecting 0.1 mmol/kg of gadodiamide (Omniscan; GE Healthcare, USA).

The volume of adenoma was calculated initially at the time of diagnosis using the Di Chiro and Nelson formula which is $4/3 \times \pi \times A.B.C/2$ or $0.52 \times A \times B \times C$; A is the maximal anteroposterior tumor dimension (depth or length) in sagittal plane, B is the maximal tumor dimension (height) in sagittal plane, and C is the maximal tumor dimension (width) in coronal plane in millimeter. The baseline signal characteristics of adenomas were assessed on coronal T2W sequence. Adenomas were divided into 2 groups based on the maximum diameter (<10 mm microadenomas and >10 mm macroadenomas). Adenomas were divided into 2 groups namely homogeneous and heterogeneous tumors depending on their T2W signal intensity. Tumors demonstrating a uniform signal intensity were labeled as homogeneous adenomas, whereas tumors that displayed mixed or different signal intensity areas within the tumor as assessed on coronal T2W images were labeled as heterogeneous. Prolactinomas which were visually very bright on T2W and hypointense on T1W were referred to as cystic prolactinomas. Baseline serum prolactin levels were recorded.

Patients with MRI-documented adenomas with raised serum prolactin levels were started on 0.25 mg of CAB twice a week for 2 weeks, and the dose was titrated stepwise to a maximum of 3 mg/week (range, 0.5-3 mg/week). These patients were serially followed up for 24 months, at 4 monthly intervals for the first 12 months and then 6 monthly intervals for the next 12 months. The dose of CAB was continuously adjusted in consideration of response, tolerance, and other clinical indicators. Serial follow-up MRIs were performed at 4, 8, 12, 18, and 24 months after starting the medical therapy. Similarly, serum prolactin levels were repeated at 4, 8, 12, 18, and 24 months. The reduction of tumor volume and serum levels of prolactin was compared at each interval examination with the baseline results, and percentage reduction of tumor volume and prolactin levels was calculated. Various characteristics of 2 groups of patients (T2W homogeneous and heterogeneous group) were recorded, and their response to treatment including percentage reduction in tumor volume and prolactin levels was evaluated in the first year after the start of CAB therapy. One year time interval was chosen for analysis to assess the early trends in the response to treatment.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21.0 software (IBM Corp.; Armonk, NY, USA) Continuous variables were expressed as means and standard deviations. Categorical variables were expressed as counts and percentages. Fisher's exact test was used for the evaluation of categorical variables, and Student's *t* test was employed for the assessment of continuous variables. $P < .05$ was considered significant.

Results

The total study population included 83 cases (52 microprolactinomas and 31 macroprolactinomas).

Characteristics of Patients with Microprolactinomas

Microprolactinomas were defined as tumors with maximal diameter of less than 10 mm on baseline MRI. Our study included 52 microprolactinomas (39; 75% females). Mean age of patients was 29.42 years (range, 16-62 years). The presenting symptoms in females were amenorrhea (22/39; 56.4%), galactorrhea (17/39; 43.5%), infertility (10/39; 25.6%), oligomenorrhea (8/39; 20.5%), hirsutism (2/39; 5%), mastalgia (2/39; 5%), and headache (1/39; 2.5%). Males presented with complaints related to erectile dysfunction (5/13; 38.4%), gynecomastia (3/13; 23%), infertility (2/13; 15.4%), and galactorrhea (2/13; 15.4%).

The mean baseline volume of microadenoma was 0.205 ± 0.112 cm^3 (Table 1). Mean adenoma volume after 24 months of treatment was 0.050 ± 0.042 cm^3. A total of 27 (51.9%) patients showed complete disappearance of adenoma at 24 months. Among them, complete disappearance of adenoma was seen in 1 (1.9%) patient at 4 months, in 3 (5.7%) at 8 months, in 11 (21.1%) at 12 months, and in 12 (23%) patients at 24 months. The remaining 25 (48.1%) patients had residual tumors at 2 years.

Table 1. Tumor Volume at Baseline and Percentage Reduction in Tumor Volume on Various Follow-Up Intervals

Scan Time	Number of Patients (n)	Tumor Volume (mm^3) on Baseline MRI, Mean (±SD)	Percentage Tumor Volume Reduction on Follow-Up MRIs, Mean (±SD)
First scan	52	205.87 (112.2)	
4 months	52	136.8 (88.3)	35.64 (17.5)
8 months	51	95.04 (72.6)	56.52 (19.5)
12 months	48	69.95 (62.6)	69.92 (19)
18 months	37	57.23 (55.6)	76.40 (18.6)
24 months	25	50.35 (42.4)	79 (13.7)

MRI, magnetic resonance imaging; SD, standard deviation.

In this study, there was approximately a 79% overall reduction in the volume of microadenoma at 24 months. Tumor volume reduction of ≥75% was noted in 82.69% of patients at 24 months, while 17.3% of patients showed less than 75% tumor reduction at 24 months. Less than 50% reduction of tumor was noted in 3.8% of the patients, while none of the patients had reduction of tumor volume of less than 40% (Table 1).

The mean baseline prolactin levels were 147.27 ± 92.91 ng/mL, while mean prolactin levels were 30 ± 25 ng/mL at 2 years. More than 75% reduction in prolactin levels was seen in 88.46% of patients, whereas a reduction of less than 75% in prolactin levels was seen in 11.53% of the patients at 24 months (Table 1). Maximum reduction of prolactin levels was noted within the first 4 months after the start of treatment with a percentage reduction of 25%. The percentage reduction was 21% from 4 to 8 months, 18% from 8 to 12 months, 12% from 12 to 18 months, and 4% from 18 to 24 months. The mean prolactin levels were 50 ng/mL at 1 year and 30 ng/mL at 2 years. The maximum prolactin level recorded at 2 years was 102 ng/Ml, and only 3 patients had a prolactin level ≥100 ng/mL at 2 years. A combined tumor volume reduction of >50% and normoprolactinemia was achieved in 47 (90.3%) patients. One microprolactinoma had developed minimal hemorrhage at 4-month follow-up MRI; however, the patient had not developed any clinical symptoms related to it.

The majority (94%) of the patients with microadenomas had their symptoms improved at the end of 24-month period. Eumenorrhea was achieved in 28/30 (93.3%) females who had presented with amenorrhea/oligomenorrhea. Galactorrhea was relieved in 18/19 (94.7%) patients. Among 13 patients who had presented with infertility, 5 (38.5%) conceived, 3 did not attempt conception, whereas 5 had not conceived till the end of the study. All 5 men who had presented with erectile dysfunction reported improvement in their symptoms.

Characteristics of Patients with Macroprolactinomas

Macroprolactinoma was defined as a tumor with a maximal diameter of at least 10 mm on baseline MRI. A total of 36 macroprolactinomas were initially enrolled in the study. Among these, 3 patients were lost to follow-up, and 2 female patients who conceived within 6 months of CAB treatment were excluded from the final analysis. Finally, in total, 31 patients who were followed for 2 years, including 19 males (61.2%), were included in the study. The mean age of the study population was 41.2 years. The presenting symptoms included reproductive dysfunction including impotence, oligomenorrhea, amenorrhea, and/or infertility (n = 21; 67.7%), headache (n = 10; 32.2%), visual field defects (n = 5; 16.1%), and galactorrhea (n = 6; 19.3%). The mean tumor volume and prolactin level at baseline were 2.29 cm^3 (range, 1.20-6.7) and 420 ng/mL (range, 178-1380), respectively (Table 2). Cavernous sinus invasion of different grades was present in 10 patients (32.2%). Two tumors were classified as cystic adenomas and 2 showed hemorrhagic change. At the last assessment, the mean tumor volume reduction was 77.6%. The tumor volume reduction at different intervals is presented in Table 2. A total of 3 (9.7%) patients showed complete disappearance of macroadenoma at 24 months. Among them, complete disappearance of adenoma was seen in 1 patient at 8 months, in another at 12 months, and in 1 at 18 months. The remaining 28 (90.3%) patients had residual tumors at 2 years. Tumor volume reduction of ≥75% was noted in 81.2% of patients at 24 months, while 18.8% of patients showed less than 75% tumor reduction at 24 months. Less than 50% reduction of tumor was noted in 6% of the patients, while none of the patients had a reduction of tumor volume of less than 25%. Two macroprolactinomas developed internal hemorrhage during the course of treatment, and 1 among them had presented clinical symptoms related to it.

The mean baseline prolactin level was 420 ± 161 ng/mL, while the mean prolactin level was 103 ± 49 ng/mL at 2 years. More than 75% reduction in prolactin levels was seen in 83.9% of patients, whereas a reduction of less than 75% in prolactin levels was seen in 16.1% of the patients at 24 months (Table 2). The break-up percentage reduction of prolactin levels is given in Table 2. A combined tumor volume reduction of >50% and normoprolactinemia was achieved in 20 (64.5%) patients.

Clinical improvement was reported in 83% of the patients with macroadenomas at 24-month period. Only 1 patient needed surgery till the end of the study for lack of adequate response and deterioration of vision.

Cabergoline dosage of 0.5-3 mg/week was well tolerated by most of the patients. Some patients observed minor adverse effects like nausea, diarrhea, and headache. No major side effect was seen in the study population.

Table 2. Serum Prolactin Levels at Different Intervals and Percentage Reduction in Serum Prolactin Levels at Various Follow-Up Intervals

Time	Number of Patients (n)	Serum Prolactin Levels (ng/mL) Mean (±SD)	Percentage Reduction in Serum Prolactin Levels on Follow-Up Mean (±SD)
Baseline	52	147.27 (92.91)	
4 months	52	106.06 (69.29)	25.69 (14.83)
8 months	52	76.02 (59.63)	46.93 (17.61)
12 months	51	50.83 (38.96)	64.40 (15.63)
18 months	48	35.32 (33.78)	76.63 (13.57)
24 months	36	30.06 (25.09)	80 (10.40)

SD, standard deviation.

T2-weighted Homogeneous Prolactinomas Versus Heterogeneous Prolactinomas

On coronal T2W MRI, adenomas were classified as homogeneous and heterogeneous. Four tumors with visible cystic and hemorrhagic changes were categorized under the heterogeneous group. The homogeneous prolactinomas (n = 51) included 38 (74.5%) microadenomas and 13 (25.5%) macroadenomas. The heterogeneous group (n = 32) included 14 (43.7%) microadenomas and 18 (56.3%) macroadenomas. Mean age and gender ratio did not differ significantly between the 2 groups ($P > .05$). The baseline tumor volumes and prolactin levels were significantly higher in the T2W heterogeneous tumors compared to the homogeneous group (both $P < .05$). After 1 year of treatment with CAB, a higher number of patients (35/51; 68.6%) showed normalization of prolactin levels in the homogeneous group compared to the heterogeneous group (9/32; 28.12%) with a statistically significant difference ($P = .0006$). A significantly higher number of patients in the homogeneous group (33/51; 64.7%) showed more than 50% reduction in tumor volume in comparison to the heterogeneous group (11/32; 31.25%) ($P = .012$). The percentage of tumor volume reduction was significantly more in homogeneous group (67.3%) compared to heterogeneous group (40.1%) ($P < .05$) (Table 3).

Discussion

The present study demonstrated that in patients with hyperprolactinemia secondary to prolactinomas, once or twice weekly low-dose CAB therapy for a long-term (up to 2 years) has excellent patient acceptability and compliance and causes complete disappearance or shrinkage of the tumor volume in the majority of patients with reduction in serum prolactin levels and amelioration of clinical symptoms. The convenient once or twice weekly dosage of CAB also makes it preferable over other dopamine agonists like BRC, quinagolide, and pergolide because these previously used drugs had to be administered twice or thrice daily and had unavoidable toxicity profiles resulting in diminished acceptability and compliance.

The results of the present study demonstrate that CAB is equally effective in reducing the volume of micro- and macroprolactinomas and in the amelioration of hyperprolactinemia with a safe side effect profile and excellent tolerability. The results of the present study are in concordance with various previous studies which have documented the effectiveness of CAB in the management of prolactinomas.[19-21] Pinzone et al[22] in a retrospective review of pituitary prolactinomas managed medically reported the restoration of normoprolactinemia in a comparable percentage of microprolactinomas and macroprolactinomas (83% and 79%, respectively).

In the present study, T2W heterogeneous prolactinomas included a higher percentage of macroadenomas and were significantly larger and more secreting compared to homogeneous tumors at baseline (all $P < .05$). After 1 year of treatment, T2W homogeneous tumors showed a better response (higher percentage of tumor volume and prolactin reduction) compared to the heterogeneous group (all $P < .05$). A recent study by Burlacu et al[17] reported that T2W heterogeneity correlated with poorer response to dopamine agonists in prolactinomas. Our results are in concordance with this study. However, we did not subdivide the homogeneous tumors as hypointense and hyperintense as reported in this study. Our findings extend the results of this previous study. Another recent study comprising 54% microprolactinomas and 46% macroprolactinomas tried to explore the clinico-radiological factors predictive of blunted response to dopamine agonists and found that male gender, larger size of tumors, prolonged time to normalization of prolactin, and cystic or hemorrhagic intra-tumoral changes on MRI were associated with a poorer response to treatment.[18] Pituitary tumors can undergo degenerative changes such as necrosis, intra-tumoral hemorrhage, fibrosis, calcification, and hyaline accumulation which leads to heterogeneous signal on imaging. These changes are more frequently seen in large prolactinomas, particularly in the sparsely granulated type. The heterogeneity of adenoma on MRI could represent histological surrogates of internal necrosis, hemorrhage, fibrosis, or hyalinization.[17] Intra-tumoral hemorrhage in prolactinomas has been reported in approximately 7% of a large series of prolactinomas preponderantly in macroadenomas, and the vast majority of them were clinically silent.[23] The prevalence of intra-tumoral hemorrhage in surgical series goes up to 18%. Tumors with a predominant cranial growth have been found to undergo hemorrhagic change more frequently presumably due to the compression of the superior hypophyseal artery.

The results of the present study support that baseline T2W signal characteristics of prolactinomas can potentially predict the behavior of tumors to pharmacological treatment and this information can help in guiding therapy in these patients.

Table 3. Comparison Between 2 Groups of Prolactinomas Based on Their Initial T2W Imaging Characteristics

Parameter	T2W Homogeneous (n = 51)	T2W Heterogeneous (n = 32)	*P*
Age (years)	29.5 (16-59)	31.3 (18-68)	>.05
Sex (male/female)	15 : 36	10 : 22	1
%age macroadenoma	13/51 (25.5)	18/32 (56.3)	.0059
Baseline prolactin level (ng/dL) (mean ± SD)	193 (99.2)	510 (167.7)	.0001
Baseline tumor volume (cm^3) (mean ± SD)	1.2 (0.48)	2.21 (1.3)	.0001
CAB dose (mg/week)	1.1 ± 0.55	1.4 ± 0.50	.0990
Prolactin level at 1 year (ng/mL) (mean ± SD)	123 (79.9)	331 (136)	.0001
Percentage tumor volume reduction at 1 year (%) (mean ± SD)	67.3	40.1	.0001
Percentage with normal prolactin at 1 year	68.6 (35/51)	28.12 (9/32)	.0006
Percentage with tumor volume reduction >50% at 1 year	64.7 (33/51)	31.25 (11/32)	.012

SD, standard deviation; T2W, T2-weighted; CAB, cabergoline.

Our study has some important limitations. The small sample size and lack of histological data to explain the heterogeneous imaging characteristics of tumors are important limitations. However, if the results of the present study are validated by a larger study, this could well serve as an important prognostic tool to guide the management of adenomas at their initial detection.

Conclusion

Long-term CAB therapy for prolactinomas is well-tolerated and has excellent efficacy in the reduction of tumor volume, normalization of prolactin excess, and causes the disappearance of clinical symptoms of hyperprolactinemia. T2-weighted imaging features of prolactinomas correlate with their clinical behavior under CAB. T2-weighted homogeneous prolactinomas had a more favorable outcome in comparison to the heterogeneous tumors.

Ethics Committee Approval: The study was approved by the ethics committee of Sher-i-Kashmir Institute of Medical Sciences.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.M., S.F., G.A.; Design – S.M., S.F., G.A.; Supervision – C.N., B.R.; Resources – S.M., G.A.; Materials – P.A., G.A., S.F., C.N.; Data Collection and/or Processing – S.M., G.A., C.N., A.P.; Analysis and/or Interpretation – P.A., C.N.; Literature Search – P.A., C.N.; Writing Manuscript – P.A., S.M.; Critical Review – P.A., C.N.

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