


Clinical Features, Therapeutic Trends, and Outcome of Giant Prolactinomas: A Single-Center Experience Over a 12-Year Period

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ABSTRACT

BACKGROUND: Management of giant prolactinomas presents a different challenge than the management of traditional prolactinomas.

OBJECTIVE: The aim of this study was to report the largest long-term single-center study of giant prolactinomas to analyze their clinical features; define epidemiological characteristics, comorbidities, complications, treatment outcomes; and to demonstrate our experience with long-term cabergoline (CAB) treatment of these giant tumors.

METHODS: A retrospective case study and clinical review of patients presenting with giant prolactinomas in the pituitary clinic at King Fahad Medical City (KFMC), Riyadh, Saudi Arabia, in the period between 2006 and 2018 were included in the study. Of the charts reviewed, 33 patients (24 men; 9 women) with age of diagnosis between 18 and 63 years (mean = 37.21 years) met the selection criteria for giant prolactinomas.

RESULT: The most common presenting features include headache (87.8%), visual defects (69.7%), and hypogonadism (51.5%). The baseline means serum prolactin (PRL) level was extremely high for both sexes (95 615.03 nmol/L), which eventually decreased by as much as 95.4% after CAB treatment. Serum PRL concentrations completely normalized in 11 patients and significantly reduced in 22 patients. The mean tumor volume at baseline was 42.87 cm³, whereas the mean posttreatment tumor volume was 3.42 cm³ (no residual tumor in 2 patients, while in others, it ranged from 0.11 to 16.7 cm³) at the last follow-up visit. The mean change in tumor volume was 88.84%. Tumor volume decreased by an average of 92% for men and 80.4% for women. One patient had no tumor size change with CAB (3.5 mg thrice a week) or radiotherapy and required surgery. The response rate (remission after medical therapy alone) in this series was 84.84%.

CONCLUSIONS: Findings reinforce results from our previous study that CAB provides dramatic clinical improvements with an excellent safety profile. The CAB should, therefore, be considered as the primary therapy for giant prolactinomas.

KEYWORDS: Giant prolactinoma, pituitary adenoma, prolactin, comorbidity, tumor, cabergoline, transsphenoidal surgery, remission

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Introduction

Pituitary tumors represent nearly 15% of all intracranial tumors.¹ Prolactinomas are the most common pituitary tumors, representing around 40% of all pituitary adenoma.^{2–4}

Most prolactinomas are small, benign, slow-growing intrasellar microadenomas (<1 cm), occur more often in women, and typically present with significant clinical sequelae due to hyperprolactinemia, including gonadal dysfunction, amenorrhea, and galactorrhea. However, prolactinomas are larger, more invasive, and more aggressive in men. Macroprolactinomas of more than 10 mm, may, however, occur particularly in young to middle-aged men, with a male-to-female proportion of around

9:1, causing mass effect symptoms.^{5–9} At the end of the spectrum, giant prolactinomas are a rare form, representing only 2% to 3% of all prolactinomas and accounting for ~0.5% of pituitary tumors.⁸ Giant prolactinomas are characterized by significant extrasellar extension and massive serum prolactin (PRL) elevations, usually with a diameter of 40 mm or more and serum PRL concentrations above 1000 µg/L (21 000 mIU/L) and no associated growth hormone (GH) or adrenocorticotrophin (ACTH) secretion; presenting with clinical symptoms induced by the hyperprolactinemia or mass effect.^{5,9}

An atypical pituitary adenoma is a rare entity characterized by its invasiveness, increased mitotic activity, excessive p53



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immunoreactivity, and a MIB-1 proliferative index greater than 3%. Patients may present with multiple recurrences. Malignant prolactinomas are rare tumors defined by the presence of cerebrospinal, meningeal, or distant metastasis.¹⁰

Familial prolactinoma includes MEN1 syndrome as a result of mutations in the MEN1 gene.¹¹ Pituitary adenomas usually found in about 40% of patients with MEN1, with the predominance of female individuals and mean age at disease occurrence of 38 years. Prolactinomas are the most frequent type in this syndrome, occur in 15% to 20%, and are usually macroadenomas.¹² Familial isolated pituitary adenoma (FIPA) with germline AIP mutations should be considered in a patient who lacked clinical evidence of MEN1 syndrome or Carney complex.¹³ AIP mutations are identified in 20.4% of patients with FIPA,¹⁴ and about 3% in a patient with sporadic pituitary adenomas.^{13,15} Patients with FIPA are younger at the time of diagnosis than patients without AIP mutations, and they typically have GH-secreting adenomas and prolactinomas, which are usually macroadenomas.¹⁶ Screening for these syndromes should be considered in young patients with large and more aggressive adenoma.¹⁶ Cabergoline (CAB) can normalize PRL levels by 69% to 75%, and at higher doses, it can decrease PRL levels by 98%, while reducing tumor size by 26% to 90%.¹⁷ In a recent series of 71 patients with giant prolactinoma, 55% of patients achieved PRL normalization and 26% had no visible tumor in the entire cohort at follow-up.¹⁸ We, as of late, reported our experience with CAB treatment in a series of 16 Arab cases with giant prolactinomas,¹⁷ where we reported a male preponderance with 10 men and 6 women and found it to provide dramatic clinical improvement with an excellent safety profile. The aim of this study was to report a long-term single-center study of a large cohort of giant prolactinoma patients to analyze their clinical features; define epidemiological characteristics, comorbidities, complications, therapeutic approach, and treatment outcome; and to demonstrate our experience with long-term CAB treatment of these giant tumors.

Patients and Methods

Patients

A retrospective case study and clinical review of patients presenting with giant prolactinomas evaluated in the pituitary clinic at King Fahad Medical City (KFMC), Riyadh, Saudi Arabia, in the period between 2006 and 2018 were included in the study.

The study was approved by the Institutional Review Board (IRB) of KFMC (approval number 17-186). A total of 33 patients (24 men; 9 women) met the selection criteria for giant prolactinomas, namely, tumor diameter more than 40 mm in at least 1 dimension and serum PRL concentration higher than 1000 µg/mL. After chart reviews, the patient's medical history, demographic features, date of diagnosis, clinical features, presenting symptoms, hormonal profile, and radiological aspects were noted.

Biochemical assessments

The hormonal assessment was based on prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH) ± Insulin-like Growth Factor 1 (IGF-1), thyroid-stimulating hormone (TSH), free thyroxin (FT4), cortisol, and adrenocorticotropic hormone (ACTH), estradiol and total testosterone. Initial serum PRL was the pretreatment documented PRL measurement, and the final serum PRL measurement was the latest documented PRL at follow-up clinical visit. Serum PRL levels were measured by electrochemiluminescence immunoassay (Elecsys Prolactin 11) (Roche Diagnostics, Indianapolis, IN, USA) at each visit. The normal range was 100 to 390 nmol/L. The PRL levels were diluted for all subjects to correct for any possible hook effects. Total testosterone was determined by electrochemiluminescence immunoassay (Elecsys Testosterone 11) (Roche Diagnostics, Indianapolis, IN, USA). Measuring range was 0.025 to 15 ng/mL (0.087-52 nmol/L).

Imaging assessments

Radiological assessments to record tumor size and extension were based on magnetic resonance imaging (MRI), which were performed with multiple planes and thin layers (3 mm). Sagittal, coronal, and axial sections were used to evaluate the tumor size. The volume was calculated using the Cavalieri principle, which takes into consideration tumor diameter measurements in 3 orthogonal planes on MRI. Tumor shrinkage was evaluated as a reduction in maximal tumor diameter compared with baseline, as well as a decrease in tumor volume. The criteria to define the tumor invasiveness were on the bases of 2 radiological classification system; Knosp classification to quantify tumor invasion of the cavernous sinus in coronal sections of MRI¹⁹ and Hardy classification, where pituitary adenomas are classified into 4 grades depending on their size and invasiveness in the sella turcica.²⁰ MRI was done before starting treatment, 6 months after starting medical therapy, and on an annual basis. The baseline and final MRI were included in the study.

Visual field

A visual field examination was performed using the Goldmann-Friedmann perimetry before treatment, 2 to 3 months after the onset of treatment and then every 6 months until findings normalized. Ophthalmic examination and visual field assessment at baseline and at the last visit as an important subjective outcome measure in all subjects.

Treatment protocol

A definite diagnosis was based on clinical presentation (headaches, visual symptoms, loss of libido, erectile dysfunction in men, oligomenorrhea or amenorrhea and galactorrhea in women, infertility, and osteoporosis in both sexes) high PRL

concentrations, and characteristic MRI pituitary features. Once the diagnosis was confirmed, all patients uniformly received dopamine agonist (DA) as primary therapy in the form of CAB at a dose of 0.25 mcg once or twice per week with the escalation of the dose if needed depending on the level of the PRL and tumor size. If PRL levels normalized, and a significant reduction in tumor volume of greater than 50% from the previous imaging was achieved, CAB doses were maintained or decreased to the lowest possible dose.

All patients were followed for a mean period of 6.3 years (range 2-13 years). Follow-up clinical visits included a clinical examination focusing on visual field examination, assessment of the PRL level, pituitary function tests, and MRI.

Definition of response to therapy

Hormonal response or remission was defined as serum PRL measurement, either lesser than or equal to 390 nmol/L (≤ 25 ng/mL) or more than 50% reduction from the baseline with at least 12 months of follow-up from the time of initial clinical visit. Similarly, the radiological response was defined as no evidence of visible tumor or more than 50% reduction of tumor from the baseline on the follow-up MRI.

Statistical analysis

Results are expressed as mean \pm SD for continuous variables and percentages (%) for frequencies. Data were analyzed using SPSS version 16.5 (SPSS Chicago, IL, USA). Differences in a patient, PRL, or tumor-related parameters by time to treatment response were calculated with Student's unpaired t-test. A *P*-value lesser than .05 was considered significant.

Result

Among 286 patients with pituitary tumors, we observed 33 cases (11.5%) which fulfilled the clinical and radiological criteria of giant prolactinomas during the study period, and these were included in our study. Among this group, 24 were men with an age range of 20 to 63 years (mean 38.13 years) at diagnosis and 9 were women with an age range of 18 to 52 years (mean 34.78 years) at diagnosis. There were more men with giant prolactinomas (24 vs 9) with a larger baseline mean diameter (4.29 cm vs 4.02 cm), greater mean baseline volume (49.88 cm³ vs 24.17 cm³, *P* = .0958) and smaller posttreatment mean diameter (1.5 vs 1.99 cm³, *P* = .05) compared with female patients. Other comparisons between sexes were not statistically significant.

The mean serum PRL concentration at the time of diagnosis (Table 1) was extremely high 95 615.03 nmol/L (range 10 000-42 5325 nmol/L). The latest PRL level was dramatically reduced in all patients, with a mean PRL change of 95.41% (range 77.77-99.99%). Baseline and posttreatment mean values of PRL and tumor volume are tabulated in Table 1.

Table 1. Baseline and posttreatment mean values of prolactin and tumor volume.

DATA	MALE	FEMALE
Age at diagnosis (years)	38.125	34.8
PRL pretreatment (nmol/L)	89 109.5	112 963.1
PRL posttreatment (nmol/L)	2503.5	2506.1
PRL % change	94.3	98.3
Nadir (months)	36	30
Pretreatment tumor volume (cm ³)	49.9	24.2
Posttreatment tumor volume (cm ³)	3.4	4.1
Tumor size % decrease	92	80.4
Time difference (months)	5.5	5.3

Abbreviation: PRL, prolactin.

Comparisons of the changes in tumor size and PRL values based on sex at pre- and posttreatment found no significant differences between men and women.

Clinical symptoms and comorbidities

Headache was the most frequent symptom reported in 29 patients (87.8%), which eventually resolved after treatment in all patients. Men presented with main concerns of headache (95.8%) and visual disturbances (70.8%), while women presented with amenorrhea (55.6%), along with headache (66.67%), visual disturbances (66.67%), and galactorrhea (66.67%).

Among the 23 patients that reported symptoms of visual changes, 8 patients presented with visual field defects (VFDs) as detected by the Goldmann-Friedmann perimetry. Six of them completely improved after treatment. Among the male patients, 18 (75%) reported decreased libido, 1 (3.4%) reported infertility, and 2 (8.3%) reported erectile dysfunctions. In all patients reported herein, endocrine evaluation performed at baseline and after treatment showed secondary hypogonadism in 48.28% (*n* = 14) of male patients; only 8 reported improvements in their sexual function after 6 to 12 months of treatment. Five female patients had amenorrhea. Nine patients had markedly low insulin-like growth factor (IGF)-I values for age and sex in the context of another pituitary hormone deficiency. Galactorrhea was reported in 8 patients, which disappeared after starting treatment. Other reported symptoms are tabulated in Table 2.

Twenty-five patients with secondary hypothyroidism continued treatment with a stable hormone profile. Secondary hypoadrenalism was found in 8 patients; all of them had a morning cortisol value lesser than 100 nmol/L, which was further confirmed by (250 μ gr) cosyntropin test. Hydrocephalus was reported in 3 patients, all of them underwent transcranial

Table 2. Pretreatment clinical symptoms in patients with giant prolactinomas.

SYMPTOMS	TOTAL, N (%)	MALE, N (%)	FEMALE, N (%)
Visual change	23 (69.7)	17 (70.8)	6 (66.67)
Headache	29 (87.8)	23 (95.8)	6 (66.67)
Seizure	2 (6.06)	2 (8.3)	0.0
Decreased libido	20 (60.6)	18 (75)	2 (22.2)
Memory loss	1 (3.03)	1 (4.2)	0.0
Personality change	2 (6.06)	2 (8.3)	0.0
Infertility	2(6.1)	1 (3.4)	1 (11.1)
Amenorrhea	5 (15.15)	–	5 (55.6)
Decreased hearing	1 (3.03)	1 (4.2)	0.0
Irregular period	7 (21.2)	–	7 (77.8)
Galactorrhea	8 (24.2)	2 (8.3)	6 (66.7)
Vomiting	2 (6.06)	1 (3.44)	1 (11.1)
Erectile dysfunction	2 (6.06)	2 (8.3)	–

Table 3. Comorbidities in patients with giant prolactinomas.

COMORBIDITIES	TOTAL, N (%)	MALE, N (%)	FEMALE, N (%)
Diabetes insipidus	1 (3.03)	None	1 (11.11)
Hypogonadism	17 (51.51)	14 (48.28)	3 (33.33)
Ischemic heart disease	2 (6.06)	2 (8.33)	None
Hypoadrenalism	8 (24.24)	5 (17.24)	3 (33.33)
Hypothyroidism	25 (75.76)	18 (62.07)	7 (77.78)
Third nerve palsy	4 (12.1)	2 (8.3)	2 (22.2)
Visual field defect	8 (24.24)	6 (25)	2 (22.22)
Hydrocephalus	3 (9.68)	3 (12.5)	0.0

partial resection surgery prior to CAB treatment with 1 requiring placement of ventriculoperitoneal shunt. Rhinorrhea (cerebrospinal fluid [CSF] leak) was seen in only 3 patients while on treatment, which was later treated with surgery in 2 and placement of a ventriculoperitoneal shunt in 1 of them. Apoplexy was reported in 5 patients. Of these, 2 patients underwent surgery due to progressive visual impairment. Other recorded pretreatment complications and morbidities (Table 3) consisted of the following: visual field defect, hypogonadism, diabetes insipidus, type 2 diabetes mellitus, and ischemic heart disease. Diabetes insipidus was reported in 1 patient, which persisted even after CAB therapy. Fragility fracture was not reported by any patient at the presentation. In the absence of fragility fracture and other risk factors for bone loss, bone mineral density scores by dual-energy X-ray absorptiometry (DXA) scan were not done in any patient. Echocardiography was done

for all patients at baseline, and every 2 years in a patient who required greater than 2 mg of CAB per week with no cardiac valvular abnormality could be documented.

Effects of CAB treatment on clinical symptoms, sexual functions, and pituitary functions

In 5 women with amenorrhea, menstruation resumed in 4 patients and galactorrhea disappeared in all patients.

In men, 14 patients had low baseline testosterone levels low (<9.9 nmol/L), and 22 patients presented with erectile dysfunction or low libido. After treatment, serum testosterone normalized in 10 patients, and sexual function improved to various degrees in 8 patients. Four patients had persistently low testosterone levels. During CAB therapy, the patients with secondary hypoadrenalism and secondary hypothyroidism did not

Table 4. Posttreatment complications.

COMPLICATIONS	N (%)	MALE, N (%)	FEMALE, N (%)
Epistaxis	2 (6.06)	0.0	2 (6.4)
CSF leak	3 (9.68)	2 (8.33)	1 (9.09)
Pituitary apoplexy	5 (16.13)	4 (16.67)	1 (9.09)

Abbreviation: CSF, cerebrospinal fluid.

Table 5. Treatment modalities of patients with giant prolactinomas.

TREATMENT MODALITY	PATIENT, N (%)
DA (CAB)	33 (100)
Surgery	5 (15.2)
Chemotherapy	0.0
Radiotherapy	4 (12.12)

Abbreviations: CAB, cabergoline; DA, dopamine agonist.

show any significant changes and continued to be treated with substitutive therapy showing a stable hormonal profile. None of the patients had either clinical or biochemical evidence of GH excess. The 8 patients that had visual field defects (24.24%) at presentation consisted primarily of bitemporal hemianopsia in addition to third nerve palsy in 4 patients secondary to compression from the tumor. There was a marked improvement in the visual field in 6 of them with a few days of starting treatment. Patients on chronic CAB therapy may present with psychiatric symptoms and compulsive behavioral changes. However, it was not seen in our series. Posttreatment complications are shown in Table 4. No patient presented with significant side effects requiring interruption or cessation of therapy. There were no deaths in this series.

Overall response to therapy

CAB served as the primary therapy for all the patients in this study. The median follow-up period was 6 years. Remission, after medical treatment was achieved in all but 5 patients, were treated with second-line treatment modalities (surgery/radiation). Cumulative remission after all the treatment modalities was achieved in 97% of the patients.

Overall, 5 patients needed surgical interventions. Three patients underwent partial trans-sphenoidal resection of the tumor either due to apoplexy, mass effect, nasal obstruction, resistance to medical therapy, or CSF leak. Two patients underwent transcranial partial resection for apoplexy and hydrocephalus. (Table 5).

Four patients underwent radiotherapy due to poor results both in terms of PRL reduction and tumor shrinkage. In our cohort, no patient received chemotherapeutic agents such as temozolomide. All patients continued to receive CAB with good response and tolerance to the medication. The rest of the

patients reported no side effects common to the drug. Table 5 tabulates the treatment modalities of the patients.

Biochemical response

Before treatment, serum PRL concentrations were extremely high in all patients, ranging from 10000 to 425325 nmol/L (mean = $95\,615.03 \pm 105\,518$). The CAB caused a significant reduction in serum PRL levels to 2504.24 ± 4380.13 nmol/L. The PRL level normalized in 11 patients (33.3%) and significantly decreased (>90%) from baseline value in 22 patients (66.67%) by the time of the most recent evaluation. Among the patients who had still not normalized PRL serum levels, the CAB dose was progressively increased with no side effects. Following treatment for all patients, the pituitary hormone remained at the same levels, and there was no evidence of increased PRL levels during the period of this study.

CAB dosage was maintained at 1.0 mg weekly in 7 patients, 1.5 mg weekly in 16 patients, 2.0 mg weekly in 5 patients, 2.5 mg weekly in 2 patients, 3.5 mg weekly in 2 patients, and 1 patient was on 10.5 mg weekly. The CAB dose of more than 2 mg per week had to be used for overall 5 patients, which resulted in a 96.47% reduction in serum PRL level and an 87.4% reduction in tumor size volume from baseline. One patient was extremely resistant to CAB dose even at 10.5 mg/week and needed surgery along with radiotherapy following which serum PRL and tumor size decreased by 87.64% and 96.66%, respectively.

The extremely high doses of CAB used on 3 patients were well-tolerated, and we noted no side effects. Patients were scheduled to at the beginning to visit the clinic every 3 to 4 months to assess response to CAB management and analyze serum PRL level at each visit.

Radiological response

A significant reduction in tumor volume was observed in all but 1 patient who demonstrated radiological and hormonal resistance to CAB despite weekly doses of 3.0 to 10.5 mg. The mean tumor volume at the time of diagnosis was 42.87 cm^3 (range $5.84\text{--}175.12\text{ cm}^3$). In all patients, a significant reduction in tumor volume was observed, which was usually evident after 6 to 12 months of therapy. The mean tumor volume at baseline 42.87 cm^3 (range $5.84\text{--}175.12\text{ cm}^3$), whereas the mean post-treatment tumor volume was 3.42 cm^3 (range $0\text{--}16.7\text{ cm}^3$) at last follow-up visit. The mean change in tumor volume was 88.83% (range $25.04\text{--}100\%$). Two patients had no residual tumor after treatment. Tumor volume decreased by an average of 92% for men and 80.4% for women. Before CAB treatment, 3 patients underwent partial transsphenoidal removal of the tumor, but the surgery had not significantly modified the tumor volume, as demonstrated by MRI at study entry. Moreover, all patients exhibited a significant decrease in tumor volume calculated from their most recent clinical evaluation and MRI (Table 1).

Discussion

In this series, we retrospectively evaluated clinical data, tumor characteristics, and clinical outcomes in 33 patients with giant prolactinomas. Giant prolactinomas are rare tumors where the exact prevalence is not known. The reported prevalence rates from various studies range from 0.5% to 4.4%.^{8,21,22} In our study, giant prolactinomas accounted for 11.5% of patients with pituitary tumors. This percentage is a little higher compared with what was reported in the literature, as our hospital is considered as a referral center for pituitary tumors. Generally, prolactinomas are more frequent in women, but they are larger, more invasive, and more aggressive in men.²³⁻²⁷ Our study concurs with the recent literature, and we found there were more men with giant prolactinomas (24 vs 9) with a larger baseline mean diameter (4.29 vs 4.02 cm³), greater mean baseline volume (49.9 vs 24.2 cm³, $P = .0958$) compared with female patients. In accord with other studies that giant prolactinomas are seen in the young population, we found nearly 38.7% of the patients were under 30 years at diagnosis. Many series showed male preponderance.^{21,22,26} The overrepresentation of women has been reported in other series.²⁸ Our study had more men with giant prolactinomas; this discrepancy maybe because of the late presentation of male patients. Management of giant prolactinomas is a huge distinct challenge because the conventional treatments used for common macroprolactinomas may not be realistically successful as these tumors have mass effects, are invasive, and mostly result in neurological complications. Treatment priority should focus on suppressing tumor growth from the encroachment of the tumor into the central structure, alleviating the neurological symptoms and other complications resulting from the tumor growth, shrinking the tumor, normalization of hyperprolactinemia, and restoration of eugonadal and sexual function.⁵ Therapeutic options usually include surgery, radiotherapy, and medical treatment. However, surgical results are not satisfactory, risky, and rarely achieve cure due to the size, location, and invasiveness of the tumor.^{29,30} Surgery is usually reserved for resistant cases, to relieve pressure symptoms and reduce the very high PRL secretion and its consequences such as apoplexy or leakage of CSF. Radiotherapy is considered when medical therapy is unsuccessful when surgery results in incomplete resection of the tumor or tumor recurrence.³¹ DAs remain the first-line medical treatment, as they have been shown to effectively normalize PRL levels, rapidly alleviate neurologic symptoms, and significantly reduce tumor volume.^{29,30,32} Among the modern medicines available, many studies show that CAB is the preferred first line of treatment that is safe, efficacious, and well-tolerated. The CAB can normalize PRL levels by 69% to 75%, and at higher doses, it can decrease PRL levels by 98%, while reducing tumor size by 26% to 90%.^{17,21,33}

Several series are in accord with the results we found on the efficacy of medical therapy. According to a prior 6-year study done in our center in a series of 16 Arab cases with giant prolactinomas,¹⁷ CAB provided dramatic clinical improvements

(reduction by 97% of PRL levels from the extremely high baseline level for both sexes and 87% reduction in tumor size) with an excellent safety profile. A 9-year Israeli study of 12 men found CAB to be effective and safe with giant prolactinomas, improve the visual field, and restore libido within 6 months of CAB therapy at a dose from 1.5 to 7 mg/week. The PRL levels were normalized in 83% of the patients within 1 to 84 months and decreased in the other 2. Tumor shrinkage was observed in 90% of patients and visual improvement in 89%. Testosterone levels returned to normal in 66.6% of patients.³³ Although our study includes women, we report similar results with serum PRL concentrations completely normalizing in 33.3% of patients and significantly decreasing (>90%) from baseline value in 66.7% of patients. Tumor volume also decreased by an average of 92% for men and 80.4% for women. A recent review of 7 series⁵ of a total of 49 patients with giant prolactinomas treated with bromocriptine (BRC) ($n = 35$) or CAB ($n = 14$), the rate of PRL normalization was 65% with 64% of patients experiencing at least 50% reduction in tumor size. In the remaining patients, around 95% PRL reduction was achieved. In a series²¹ of 10 giant prolactinomas in men, treated with CAB serum PRL decreased by 96% from the baseline with persistent normalization achieved in 50% of patients within 3 to 6 months of treatment (mean duration of treatment 38.9 months). Tumor shrinkage was achieved after 12 months in 90% of patients, with a volume reduction of greater than 95% in 3, 50% in 4, and 25% in 2 patients. In other series of 10 patients (mean duration of follow-up of 6.7 years), treatment with BRC in 90% of the patients provided 99.8% decrease in serum PRL over the follow-up period with reductions in tumor volume up to 69% in greater than 90% of the patients.⁸ In a recent large series of 71 patients of giant prolactinoma, the complete biochemical response by normalization of PRL was seen in 55% of the cases. These were also found to be more sensitive to CAB, requiring lesser doses compared with those with an incomplete response. The complete structural response was seen in 26% of the cases. Although 74% of the patients had the persistent structural disease, 91% of them showed at least a 65% reduction in tumor volume.¹⁸ Our study concurs with all these findings, and we found the mean change in tumor volume as 88.8%. Two patients had no residual tumor after treatment. The tumor shrinkage was greater than 95% in 60.6% of patients. Due to an excellent safety profile, efficient results, and tolerance, CAB should be considered as the primary therapy for giant prolactinomas. The optimal dose and duration of DA therapy for giant prolactinoma are unclear, but the dose of CAB can be safely increased as long as the patient tolerates it without any adverse effects,⁵ and the treatment is expected to be lifelong because rapid tumor regrowth has been reported on withdrawing treatment.²⁶ Several case reports have reported on long-term follow-up in patients with CAB.^{8,34-37} A case report³⁶ of a young boy followed-up for 21 years reported

highly beneficial effects of high doses of CAB in the treatment of his giant prolactinoma, which was resistant to DAs or bromocriptine. The MRI showed that the tumor became progressively cystic and disappeared, but a normal pituitary gland was observed despite a partially empty sella. We have followed 2 patients for 13 years and another patient for 11 years, the median follow-up duration was 6 years, and no evidence of tumor recurrence in any patient based on either MRI images or increased PRL levels occurred during the period of this study. It should be noted that our study has some limitations. The study design was retrospective as it was based on medical record data—furthermore, the single-center and tertiary approach of complex cases that limits the generalizability of the study treatment approach and outcome.

Conclusions

CAB therapy appears to be effective and safe for the treatment of giant prolactinomas even when administered long term in moderately high dosages. Our study has provided critically needed information to allow appropriate measures to be implemented to address health priorities not only to predict prognosis, to inhibit tumor growth, and to destroy the tumor cells but also to prevent the development of the tumor with CAB. Our study reinforces our previous findings that CAB should be the first-line therapy before surgery for aggressive prolactinomas even in patients with visual field defects.

Author Contributions

MHA contributed to study design; MHA, MMA, and BMB contributed to data collection; MHA and BMB contributed to data analysis; MHA and BMB wrote first draft of manuscript; MHA, MMA, AAA, and BMB contributed to writing of manuscript; all authors agree with Manuscript result and conclusion; MHA, NA, SA, OA, and FA made critical revision and approved final version; and all authors reviewed and approved of the final manuscript.

Ethical Approval

This study was approved by the Institutional Review Board of King Fahad Medical City, Riyadh, Saudi Arabia (IRB 17-186).

Consent

The Institutional Review Board of King Fahad Medical City waived the need to obtain consent for the collection, analysis, and publication of the retrospectively obtained and anonymized data due to the nature of the study.

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