Original Article

Response to Treatment in a sample of Iraqi Patients with Prolactinoma

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Abstract

Background: Hyperprolactinemia is a common endocrine abnormality caused by physiological factors like pregnancy and lactation, drug-induced factors like antipsychotics, pituitary adenomas that secrete prolactin, or stalk compression or section that reduces dopamine inhibition. Dopamine agonists cure most prolactinomas. **Objectives:** To assess response to treatment in micro versus macroprolactinoma. **Materials and Methods:** A total of 35 patients (20 female and 15 male) with documented hyperprolactinemia (serum prolactin above the assay-specific reference range) due to prolactin-secreting pituitary adenoma attending the national diabetes center in Baghdad from April 2019 to March 2020 were selected. For each patient, we were recorded clinical presentation, drug history, age, body mass index, prolactin, T4, TSH, and pituitary MRI. After at least 6 months of therapy, prolactinoma patients were examined for cabergoline dosage, duration, and clinical, biochemical, and radiological response. **Results:** Cabergoline treatment with a dosage of 0.5–2.5 mg/week and a period of 6–52 months restores gonadal function and libido in most prolactinoma patients, with a stronger but nonsignificant response in micro vs macroprolactinoma (87.5% vs. 57% respectively). Cabergoline normalized menses in all microprolactinoma patients and 87.5% of macropros. Normalization of prolactin levels in 80% of prolactinoma patients, with microprolactinoma responding 95% vs 60%. gender, treatment length, or age did not affect prolactin response. 50% of surgery-radiotherapy patients experienced cabergoline-induced prolactin normalization, compared to 86% of medical therapy-only patients. Cabergoline shrank tumors in 74% of patients (80% in micro vs. 66% in macro), regardless of age, gender, length of treatment, or prior surgery/radiotherapy. **Conclusion:** patients with prolactinoma, cabergoline-induced clinical, biochemical, and radiological improvement in the majority of patients.

Keywords: Asample, cabergolin, Iraqi, response, treatment

Introduction

Prolactin is a crucial hormone produced by the anterior pituitary gland, which has various effects on the body's systems, particularly the reproductive system.[1,2] Hyperprolactinemia, characterized by prolactin levels above the gender-specific normal range, is a common endocrine issue worldwide.[3-6] It is more prevalent in females, and its incidence has risen over the past two decades.[7] Hyperprolactinemia can lead to menstrual disorders, gynecomastia, decreased libido, impotence, and infertility.[8] It has been shown to lower prolactin levels in approximately 90% of people with prolactinomas, often to a normal level, and usually decreases the size of micro- and macroadenomas.[9,10] Cabergoline is better tolerated than bromocriptine, with fewer side effects and more convenient dosing schedules.[11] It has also been reported to be effective in treating prolactinomas during pregnancy, with minimal risk of spontaneous abortion, congenital malformations, or menstrual abnormalities.[3,12] The aim of this study is to assess the response to treatment in patients with prolactinoma. Cabergoline, a dopamine agonist, is an effective treatment option for prolactinomas. And to

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differentiate between micro- and macroprolactinoma regarding response to cabergoline.

Materials and Methods

Cross-sectional comparative study of 35 patients (20 male and 15 male) prolactin-secreting pituitary adenoma with documented hyperprolactinemia (serum prolactin above the assay-specific reference range) attending the national diabetes center in Baghdad during the period from April 2019 to March 2020 were selected with age range between 23 and 42. For every patient, we were recorded his clinical presentation, Drug history, age, and body mass index. Prolactinomas were diagnosed based on elevated prolactin levels and evidence of pituitary adenomas from magnetic resonance imaging (MRI) scans, a pituitary adenoma with a diameter of less than 1 cm was defined as microprolactinoma and one above 1 cm in diameter as macroprolactinoma. In patients with prolactinoma, the dose of cabergoline, duration of treatment, the response to cabergoline (clinical, biochemical, and radiological response) after at least 6 months of treatment prospectively or retrospectively was evaluated. For clinical response in female resolution of galactorrhea, restoration of menses considered responsive, while resolution of erectile dysfunction in male is considered responsive, for both sexes resolution of headache, visual symptom and restoration of fertility also evaluated. For biochemical response recording basal prolactin level and nadir prolactin after cabergolin therapy, patient considered responsive to cabergolin when prolactin level decreased to normal range after treatment. inclusion all patient with hyper prolactinoma with pituitary adenoma in MRI, exclusion patient with prolactinoma with no pituitary adenoma in MRI regarding radiological response we were record initial pituitary MRI and final MRI after at least 6 months of treatment with cabergolin and response categorized into 5 groups according to reduction in maximal diameter of the adenoma, (I). disappearance of adenoma (II). Shrinkage >50% in maximal diameter (III). shrinkage <50% in maximal diameter (IV). No response (nochange in adenoma size) (V). empty sella.

Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25 continues variables presented as mean, standard deviation or median and range categoral data presented by frequency and percentage Chi-square test was used to find the association between categorical variables Pearson correlation coefficient was used to correlate between initial prolactin level and nadir prolactin after treatment, and to correlate between initial prolactin level and dose of cabergoline, a level of P value of <0.05 was considered significant.

Ethical approval

Procedures involving human participants followed the ethical guidelines outlined by the Ministry of Health in Iraq. All participants gave informed consent after receiving a detailed explanation of the aim of study, procedures, potential risks, and benefits. Attendants were assured of their voluntary participation and the confidentiality of their personal information.

Results

Demographic Characteristics of patients with prolactinoma treated by cabergoline 35 patients prolactin-secreting pituitary adenoma, 20 patients with micro adenoma, and 15 patients with macroadenoma. The mean age of microprolactinoma was 31.3 ± 8.2 years, for macroprolactinoma mean age was 31.4 ± 11.7 mean baseline s prolactin level for microprolactinoma was 121.45 ± 53.49, and for macroprolactinoma was 374.5 ± 163.7. Table 1 show that there is no statistically significant difference between macro and microprolactinoma by age, number of patients, and gender distribution. However, there was significant difference in mean prolactin level between macro and microprolactinoma. All patients received cabergoline in Median weekly dose of 1 mg with range of (0.5-2.5) with median duration of 18 months and duration range of (6–52) months. In patients with microadenoma, most patients are female (65%) while in macroadenoma there is nearly equal gender distribution.

Association of radiological response and adenoma size: There was significant association between adenoma size and radiological response. 80% of microadenoma had some degree of reduction in tumor size versus 66% of macroadenoma, overall 74% of patients show some reduction in tumor size [Table 2].

Association of radiological response with gender, duration of treatment, age, additional therapy (surgery ± radiotherapy). There was no significant association of radiological response with gender, duration of treatment, age, additional therapy (surgery ± radiotherapy).

A total of 80% (28 patients) shows normalization of serum prolactin after cabergoline therapy, while 20% (7)

Table 1: Characteristics of patients with prolactinoma treated by cabergolin

	Micro	Macro	*P* value
Total no	20	15	0.31
Female	13	7	0.17
Male	7	8	0.79
Age (mean ± sd) year	31.3 ± 8.2	31.4 ± 11.7	0.97
S prolactin initial (mean ± sd) ng/mL	121.45 ± 53.49	374.5 ± 163.7	<0.0001

show failure of normalization despite reduction of the level [Figure 1].

Discussion

In the current study, the mean basal prolactin in patients with macroadenoma (374.5 ± 163.7 ng/mL) was significantly higher than other causes of hyperprolactinemia, the level significantly higher in male than female probably because most females had microprolactinoma [Table 3]. Regarding demographic characteristics of prolactinoma, in our current study we have 66.6% were female while 33.3% were male with mean age of 31.3 ± 8.2 years for microprolactinoma, and 31.4 ± 11.7 years for macroprolactinoma with most patients (82%) presented before age of 40. Other study by Colao *et al.*[12] shows equivalent gender distribution with mean age of (32.2 ± 11.5) years in females and (35.0 ± 13.5) years in males. In our study in patients with microadenoma most patients are female (65%) while in macroadenoma there is nearly equal gender distribution. Microadenoma are found, more frequently in women, while it is still questioned whether macroprolactinomas are more frequent in men. Some studies have reported an equal distribution of macroprolactinomas between genders, others have found higher prevalence in men[13] or in women[14,15] in our study (17.14%) received additional treatments (surgery ± radiotherapy) in addition to cabergoline [Table 4]. Median weekly dose of cabergoline was 1 mg with range of (0.5–2.5) with median duration of 18 months and duration range of (6–52) months, in aseries by Verhelst *et al.* (goline was 1.0 mg/week, the median cabergoline dose was 0.5 mg/week at the end of the evaluation period. In the cabergoline-resistant patients, the dose of cabergoline was increased to a median of 3.5 mg/week (range, 1.5–7.0 mg/week). This analysis of patient response to Cabergoline treatment for prolactinomas displays a significant degree of success in

Table 2: Association of prolactinoma size with prolactin response

	Responsive	Non responsive	Total
Microadenoma count, %	19 (67.85%)	1 (14.28%)	20 (57.14%)
Macroadenoma count, %	9 (32.14%)	6 (85.71%)	15 (42.85%)
Total count, %	28 (100%)	7 (100%)	35 (100%)

P value = 0.009 (significant)

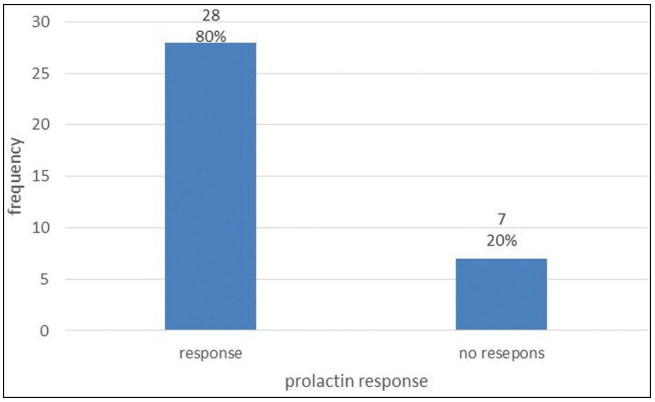

Figure 1: Prolactin response distribution

Table 3: Association between gender and prolactin response

	Responsive	Non responsive	Total
Male count, %	10 (35.71%)	5 (71.4%)	15 (42.85%)
Female count, %	18 (64.28%)	2 (28.57%)	20 (57.14%)
Total count, %	28 (100%)	7 (100%)	35 (100%)

Prolatinoma are more responsive than macroprolactinoma and the difference is significant (*P* value = 0.009), 95% of patients with microadenoma are responsive, while only 60% of patients with macroadenoma are responsive

P value = 0.009 (significant)

Table 4: The relationship between radiological response and adenoma size

	Disappearance of adenoma	Shrinkage>50%	Shrinkage<50%	No change in size	Empty sella	Total
Microadenoma Count, %	8 (100%)	6 (54.54%)	2 (28.57%)	3 (42.85%)	1 (50%)	20 (57.14%)
Macroadenoma Count %	0	5 (45.45%)	5 (71.42%)	4 (57.14%)	1 (50%)	15 (42.85%)
Total count, percentage	8 (100%)	11 (100%)	7 (100%)	7 (100%)	2 (100%)	35 (100%)

P value = 0.0014 (significant)

Table 5 Association of radiological response and gender

	Disappearance of adenoma	Shrinkage > 50%	Shrinkage < 50%	No change in size	Empty sella	Total
Male count, %	2 (25%)	3, (27.27%)	5, (71.42%)	4, (57.14%)	1, (50%)	15, (42.85%)
Female count, %	6 (75%)	8 (72.72%)	2 (28.75%)	3 (42.85%)	1 (50%)	20 (57.14%)
Total count, %	8 (100%)	11 (100%)	7 (100%)	7 (100%)	2 (100%)	35 (100%)

P value = 0.164

both symptom resolution, and prolactin normalization, particularly in patients with microprolactinomas. The response appears to be influenced by the size of the adenoma and the baseline prolactin levels, but gender and age seem to have less impact [Table 5]. These findings are in line with studies by Verhelst *et al*[16] and Colao *et al*,[17] where a high rate of symptom normalization and prolactin level normalization was reported. Microadenomas demonstrated a better response to Cabergoline therapy than macroadenomas, as was similarly observed in the studies by Verhelst *et al.*[16] Colao *et al.*[17] and other studies.[18-20] The difference was significant and reflected in restoration of gonadal function, libido, cessation of galactorrhea, headache relief, and normalization of prolactin levels. Visual symptoms were still persistent in some patients with macroadenomas, possibly due to irreversible optic chiasm damage or inadequate shrinkage of the adenoma. This aligns with results from Verhelst *et al*.[16] and Colao *et al*.[17] where normalization of visual fields was demonstrated in a significant number of patients but was not universal. Patients who underwent surgery and/or radiotherapy for resistant or invasive macroprolactinomas had less success with prolactin normalization on cabergoline therapy compared to those on cabergoline only. This was somewhat different from the results reported by Primeau *et al*.[21] and Hamilton *et al*,[22] and Vilar *et al*,[23]where surgery resulted in a normalization of PRL in a higher percentage of patients. Radiologically, a majority of patients exhibited some degree of tumor shrinkage with a significant association between adenoma size and radiological response. This corroborates the findings of Verhelst *et al.*[16] Colao *et al*.[17] In comparison with Bromocriptine, an older dopamine agonist, Cabergoline proved to be more effective in achieving normoprolactinemia according to a study conducted in Mosul, Iraq,[24]and agreed with resent study by Mariana *et al.*[25] which states that cabergoline proved to be the safest drug. Thus, the therapeutic choice considering the results obtained favors cabergoline as the first line of treatment for hyperprolactinemia.[26,27]

Conclusion

Cabergoline was significantly effective therapy in patients with prolactinoma inducing clinical remission, prolactin normalization and tumor shrinkage in the majority of patients.

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Conflicts of interest

There are no conflicts of interest.

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