

## **Manifestations of Hyperprolactinoma and its Management by Bromocriptine and Cabergoline**

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*Abstract.* This is a prospective study analyzing gender differences in the presentation of hyperprolactinemia as well as the efficacy and tolerance to cabergoline and bromocriptine. Thirty-six patients (23 women, 13 men) were recruited and divided into two groups; Group One received bromocriptine and Group Two received cabergoline for three months. The prolactin level was measured before and after treatment in both groups. Galactorrhea and infertility were more common symptoms in women; however, 100% of men with micro or macroprolactinoma had libido disturbances. The prolactin level was higher in men than in women whether they exhibited macro ( $7640 \pm 80$  vs.  $6230 \pm 71$  ng/mL) or microprolactinomas ( $6167 \pm 895$  vs.  $5998 \pm 775$  ng/mL). The prolactin level was significantly higher in women with non-tumor hyperprolactinemia ( $3390 \pm 164$  vs.  $1279 \pm 53$ ,  $p = 0.038$ ). The mean serum prolactin level was significantly decreased in both groups whether they received bromocriptine or cabergoline ( $5790 \pm 370$  vs.  $2725 \pm 124$  ng/mL;  $p = 0.001$ ). The prolactin reduction was more prominent in the cabergoline group whether in men or women, than in the bromocriptine group at the end of the three months of treatment ( $5791 \pm 723$  vs.  $1725 \pm 318$  ng/mL;  $p = 0.001$ ).

*Keywords:* Hyperprolactinemia, Prolactinomas, Bromocriptine, Cabergoline.

### **Introduction**

Prolactinomas represent the most common type of pituitary tumor<sup>[1]</sup>, however, they are relatively rare in males as more than 70% of the cases occur in women. Gender differences with regards to tumor size also exist

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in hyperprolactinemia; microadenomas are commonly found in women, while macroadenomas are more commonly found in men<sup>[2]</sup>. Women with minor elevations in serum prolactin levels often have classic symptoms of ovulatory dysfunction in the form of amenorrhea-galactorrhea syndrome. This facilitates early diagnosis in women<sup>[3]</sup>. Conversely, in men with hypogonadism symptoms of a decreased libido, sexual dysfunction and abnormal semen analysis are found. This is often overlooked and the diagnosis is often delayed<sup>[4]</sup>. The delay in diagnosis was suggested not to be the only difference between men and women<sup>[5]</sup>. Rapidly growing prolactinomas with increased markers of cellular proliferation have recently been reported to occur more often in men, suggesting more aggressive prolactinomas in men compared to women<sup>[6]</sup>.

Prolactinomas can be treated with drug therapy, surgery, or radiation therapy. Surgical resection of the adenoma is usually associated with a risk of recurrence in all patients. Hyperprolactinemia recurs one to five years after surgery in 10%-50% of patients with microprolactinomas and in 20%-90% of patients with macroprolactinomas<sup>[7]</sup>. Radiotherapy rarely results in the restoration of normal serum prolactin concentrations and therefore is generally not considered as a primary treatment for prolactinomas. For this reason, it is reserved for patients with tumors that persistently grow despite medical or surgical treatment<sup>[8]</sup>.

The standard treatment of hyperprolactinemia is the semisynthetic ergot alkaloid bromocriptine, which was introduced in 1971. It is an orally active dopamine agonist that not only inhibits the synthesis and secretion of prolactin but also reduces cellular DNA synthesis and tumor growth. Because of its short half-life, bromocriptine must be given two or three times daily. It is a cheap drug; however, it has some adverse effects such as headache, dizziness and nausea, and cannot be tolerated by 10% of patients. In addition, bromocriptine is not sufficient to normalize hyperprolactinemia in some patients<sup>[9]</sup>. Cabergoline is another potent ergot derivative that selectively binds to dopamine D2 receptors and has a long plasma half-life that enables once or twice – weekly administrations<sup>[10]</sup>. Cabergoline in doses of 0.5 to 1 mg twice weekly can normalize the serum prolactin in 83% of patients<sup>[11]</sup>.

The aim of this prospective study was to investigate gender differences in the etiology, clinical, biochemical and radiological

presentations of hyperprolactinemia. The efficacy of cabergoline to the standard regimen of bromocriptine was also compared. The dopamine agonists were given for three months in two groups of patients with microprolactinomas, macroprolactinomas or idiopathic hyperprolactinemia in a series of patients attending the medical clinic at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia.

### **Methodology**

Data from 36 patients attending the medical clinic KAUH in Jeddah with the diagnosis of hyperprolactinemia confirmed by immunoradiometric assays were included in the study. The diagnostic criteria for macroprolactinomas included a mean serum prolactin level (PRL) levels of at least 200 ng/mL and pituitary tumor  $\geq 1$  cm in diameter on computerized tomography (CT) or magnetic resonance imaging (MRI) scans; for microprolactinomas serum PRL levels  $\leq 200$  ng/mL and pituitary tumor  $< 1$  cm in diameter; for non-tumor hyperprolactinemia, serum prolactin level was above normal with a normal pituitary at MRI, with no other explanation for increased prolactin such as primary hypothyroidism or drug-induced hyperprolactinemia.

**Hormone Measurements:** Hormone measurements were performed in the hospital laboratory using standard radioimmunoassay (RIA) method using commercial kits. Serum prolactin was measured before and at the end of the study. The upper limit of normal range for PRL was 175 ng/mL for men and 225 ng/mL for women.

**Radiology:** MRI using the maximum craniocaudal diameter obtained in coronal sections evaluated tumor size. Tumors larger than 4 cm in diameter were called giant tumors. The term invasive was restricted to adenomas showing cavernous sinus invasion at radiological evaluation or at surgery. The radiological criterion used for sinus invasion was visualization of the tumor extending to the lateral margin of the carotid artery and surrounding it.

**Visual Perimetry:** In all macroprolactinomas, the assessment of visual field using Goldmann-Friedmann perimetry was performed.

**Protocol of Medical Treatment:** Thirty-four patients with hyperprolactinemia, whose serum prolactin level was above normal limit on two occasions, were assigned to one of two groups. Group One

received bromocriptine and Group Two received cabergoline for three months. Twelve patients (9 women, 3 men) received bromocriptine. Twenty-two patients (13 women, 9 men) received cabergoline. Bromocriptine was started at a dose of 2.5 mg twice daily, and cabergoline at a dose of 0.25 mg twice weekly. Subsequently, the dose of bromocriptine was increased to 5 mg twice daily and cabergoline to 0.5 mg twice weekly in the third week of the study and was continued until the end of the study.

**Statistical Analysis:** Data was reported as mean  $\pm$  SD. The statistical analysis was performed with the Statistical Package for Social Sciences program (SPSS) for Windows using analysis of variance of the frequency of observations between men and women compared by  $\chi^2$  tests and Fischer's exact probability where appropriate. The level of significance was set at  $p < 0.05$ .

## Results

Basal clinical characteristics in men and women are shown in Table 1. Macroprolactinomas were more common in men than women (30% vs. 17.3%); similarly, microprolactinomas were more frequent in men than women (66% vs. 53%); however, non-tumor hyperprolactinemia (26% vs. 15%) were more frequent in women (Table 1).

**Table 1. Baseline number of patients in bromocriptine and cabergoline groups.**

Parameter	Bromocriptine	Cabergoline
No. of Patients	12	22
Men	3	9
Women	9	13
Microprolactinomas	8	12
Macroprolactinomas	3	5
Non tumor Hyperprolactinemia	1	5

**Visual Field Defect:** Amongst individuals with macroprolactinoma, 40% of the men had visual field defect (one had tunnel vision and the second one had bi-temporal hemianopia. However, none of the women with macroprolactinomas had visual field defect.

**Prolactin Level:** The prolactin level was not significantly higher in men than women bearing either macro- or microprolactinomas. However, serum prolactin level was significantly higher in women with

non-tumor hyperprolactinemia compared to men (3390 vs. 1279 ng/mL) with  $p = 0.038$  (Table 2).

**Table 2. Patient's profile of the study expressed as means  $\pm$  S.D.**

Parameter	Women	Men	p Value
Total number of patients	23	13	
Mean $\pm$ SD	36 $\pm$ 10	41 $\pm$ 11	0.19
<b>Macroprolactinomas</b>	4	4	
Mean age $\pm$ SD	35 $\pm$ 5.5	41 $\pm$ 8.5	0.4
Basal prolactin level	6230 $\pm$ 71	7640 $\pm$ 80	0.66
Maximum tumor diameter	19.5 $\pm$ 4	21 $\pm$ 6	0.7
<b>Microprolactinomas</b>	12	8	
Mean age $\pm$ SD	37 $\pm$ 12	44 $\pm$ 14	0.25
Basal prolactin level	5998 $\pm$ 775	6167 $\pm$ 895	0.87
Maximum tumor diameter	2.25 $\pm$ 0.88	3.9 $\pm$ 2	0.05
<b>Non tumor hyperprolactinemia</b>	6	2	
Mean age $\pm$ SD	31 $\pm$ 7	40 $\pm$ 12	0.107
Basal prolactin level (ng/mL)	3390 $\pm$ 164	1279 $\pm$ 53	0.038

**Tumor Diameter:** Maximum tumor diameter was not significantly higher in men with macroprolactinomas compared to their female counterparts. However, it was significantly larger in men with microprolactinomas compared to women (p value 0.05) (Table 2).

**Clinical Presentations:** Galactorrhea was reported in both micro and macroprolactinomas, while infertility was more common in women. Panhypopituitarism was reported only in macroprolactinemia and was more common in men. Almost all men with micro or macroprolactinomas had libido disturbances (Table 3).

**Comparison of the Effect of Cabergoline and Bromocriptine on Prolactin Level:** Mean serum prolactin levels were significantly decreased in both groups (5790  $\pm$  370 vs. 2725  $\pm$  124,  $p = 0.0010$ ). The prolactin reduction after the treatment was more prominent in the cabergoline group than in the bromocriptine group at the end of the three months of treatment (cabergoline reduction was 5791  $\pm$  723 vs. 1725  $\pm$  318 ( $p = 0.001$ ) compared with bromocriptine (4025  $\pm$  301 vs. 2753  $\pm$  233, p value 0.33) (Table 4). The rate of normalization of serum prolactin was higher in the cabergoline group (14 patients, 63%) than in bromocriptine group (5 patients, 41%). Adverse effects were less frequent in the cabergoline group than in bromocriptine group. Five

patients (40%) in the bromocriptine group reported drug related adverse effects such as dizziness and nausea. Yet, only three patients (13.6%) in the cabergoline group complained of dizziness. Adverse effects generally occurred in the first week of treatment and resolved with time. However no patients stopped their treatment during the period of study.

**Table 3. Clinical presentations: Presenting symptoms expressed as the number of individual patients with prevalence in percentage.**

Parameter	Women	Men
<b>Macroprolactinomas</b>	4	4
Galactorrhea/Gynecomastia	1 (25%)	0
Infertility	3 (75%)	2 (50%)
Irregular period	3(75%)	–
Libido disturbance	–	3(75%)
Panhypopituitarism	2(50%)	3 (75%)
<b>Microprolactinomas</b>	12	8
Galactorrhea	5 (41%)	1 (12.5%)
Infertility	5 (41%)	2 (25%)
Irregular period	8(66%)	–
Libido disturbance	–	8 (100%)
Gynecomastia	–	1 (12.5%)
Non tumor hyperprolactinemia	6	2
Galactorrhea	1 (16.6%)	–
Infertility	3 (50%)	1 (50%)
Irregular period	5 (83.3%)	–
Libido disturbance	–	2 (100%)

**Table 4. Changes in serum prolactin levels (means  $\pm$  S.D) in the bromocriptine and cabergoline group before and after the study.**

Parameter	Prolactin level (ng/ml) before treatment	Prolactin level (ng/ml) after treatment	p Value
All Patients	5790 $\pm$ 370	2725 $\pm$ 124	0.001
Bromocriptine Group	4025 $\pm$ 301	2753 $\pm$ 233	0.33
Cabergoline Group	5791 $\pm$ 732	1725 $\pm$ 318	0.001

## Discussion

Gender differences in the etiology and clinical presentation of hyperprolactinemia in the two groups were observed. There was also a difference in the tumor diameter by MRI between men and women. Non-tumor hyperprolactinemia was less frequent than micro- and

macroprolactinomas. Microprolactinomas were more frequent in men in our study group; however, most studies have found microprolactinomas to be more frequent in women<sup>[2]</sup>. Macroprolactinomas were more frequent in men. The frequency of macroprolactinomas in men remains controversial in the literature. In fact, some studies have reported equal distribution of macroprolactinomas between genders; others have found a higher prevalence in men compared to women<sup>[12]</sup>.

There was no significant difference in the age at presentation in men and women with microprolactinomas or macroprolactinomas. Age at presentation for men in our study was 40 years or older, which was similar to that reported by other series like Pinzone *et al.* and Berezin *et al.*<sup>[13,14]</sup>.

Clinical symptoms at presentation differed according to gender. Infertility and galactorrhea were more frequent in women. Libido disturbances were reported in almost 100% of male patients, while interestingly, no women complained of this symptom. As expected, it was found that hypopituitarism and visual field defects were frequent in patients with macroprolactinomas than those with microprolactinomas. It was also observed more frequently in men with macroprolactinomas than in women<sup>[15,16]</sup>.

In previous studies, tumor size did not seem to be associated with duration of symptoms, and the patient's age did not correlate with tumor size in either micro or macroprolactinomas<sup>[17]</sup>. It has been suggested that macroprolactinomas have more aggressive growth characteristics in men compared with women, since markers of cellular proliferation such as Ki-67 and proliferation cell nuclear antigen were more heavily expressed in prolactinomas growing in men than those in women<sup>[18]</sup>. However, the possibility that gender-related factors modify the rate of tumor growth cannot be ruled out by the results of this study. It has not been found that there was any connection between the severities of neurological signs as expression of tumor invasiveness according to gender. This study has noted that men had larger tumors especially with microprolactinomas, which also correlated with a higher prolactin level in men compared to women<sup>[19,20]</sup>.

This was a prospective, randomized study comparing the efficacy and tolerability of cabergoline and bromocriptine in patients with hyperprolactinemia secondary to microprolactinomas, macroprolactin-

omas or idiopathic at KAUH. The shortcomings of this study are the small number of patients and the short duration of treatment. Mean serum prolactin levels were significantly decreased in all patients after treatment with a p value of 0.001. Prolactin reduction was more prominent in the cabergoline group than in the bromocriptine group at the end of three months of treatment with a significant p value of 0.001. Three months treatment resulted in a higher rate of normalization of serum prolactin in the cabergoline group, in comparison with the bromocriptine group (63% vs. 40%). These results clearly indicate that cabergoline is superior to bromocriptine in terms of both normalization rate and the mean suppressibility of elevated prolactin<sup>[21,22]</sup>. In some studies, tumor shrinkage has been reported. Because this study was relatively short-term (only three months), MRI imaging was not repeated at the end of the study<sup>[23]</sup>. More side effects were observed in the bromocriptine group than the cabergoline group (40% vs. 16.6%)<sup>[24,25]</sup>. The side effects in these patients were much lower than other studies, which may be explained by lowering the doses of bromocriptine and cabergoline<sup>[26]</sup>. The outcome of treatment evaluated according to the etiology and gender was similar in both men and women. The corresponding data reiterates the concept that cabergoline is an effective drug in men and women. Cabergoline is more effective and tolerable than bromocriptine at usual treated doses.

### Conclusion

In patients with idiopathic, microprolactinomas or macroprolactinomas related hyperprolactinemia, in this study has shown that cabergoline is more effective and better tolerated than bromocriptine. Furthermore, its long-lasting effect makes it easy to use. For these reasons, cabergoline appears to be a reasonable alternative for patients in whom bromocriptine is not sufficiently efficacious or not well tolerated. For patients with financial difficulties, bromocriptine may be used as it is a cheaper alternative.

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## أعراض ارتفاع هرمون الحليب وعلاجه

فايزة عبدالعزيز قاري

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المستخلص. الدراسة مستقبلية لمقارنة الاختلاف الجنسي من الناحية الإكلينيكية في ارتفاع هرمون الحليب، ومقارنة تأثير دواء الكربورغلين مع البرموكربتاتين في هرمون الحليب. قسم ٣٦ مريضا مصابون بارتفاع هرمون الحليب إلى مجموعتين. المجموعة الأولى عولجت بدواء البرموكربتاتين، والمجموعة الثانية بدواء الكربورغلين لمدة ثلاثة أشهر. تم قياس هرمون الحليب عند بدء وانتهاء الدراسة في نسبة الهرمون. العقم وإفراز الحليب من الثدي من الأعراض الأكثر شيوعا بين النساء. وسجل الضعف الجنسي بنسبة ١٠٠٪ بين الرجال المصابين بارتفاع هرمون الحليب. كانت نسبة هرمون الحليب أكثر ارتفاعا بين الرجال مقارنة بالسيدات، سواء بسبب الورم الحليبي المتضخم أو الورم الحليبي الصغير في الدماغ (6230 ± 71 vs. 7640 ± 80 ng/mL). (5998 ± 775 vs. 6167 ± 895 ng/mL).

سجلت نسبة ارتفاع هورمون الحليب ارتفاعاً ذا دلالة إحصائية مميزة عن السيدات المصابات بارتفاع هورمون الحليب غير الورمي مقارنة بالرجال (p=) 1279 ± 53 vs. 3390 ± 164 (0.038). سجل انخفاض هورمون الحليب بنسبة ذات دلالة إحصائية في المجموعتين اللتين تلقتا علاجاً بالكربورغلين أو البروموكربتاتين (p =) 2725 ± 124 ng/mL vs. 5790 ± 370 (0.001). كانت نسبة انخفاض هرمون الحليب بنسبة إحصائية

مميزة في مجموعة الكربورغلين سواء في الرجال أو السيدات،  
مقارنة بنسبة انخفاض هرمون الحليب مع دواء بروموكربتئين في  
نهاية الشهر الثالث من العلاج ( $1725 \pm 318$  vs.  $5791 \pm 723$  ng/mL ;  $p = 0.001$ ).