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Evaluation of Hyperandrogenemia in Women with Prolactinoma

Prolaktinomalı Kadınlarda Hiperandrojenizmin Değerlendirilmesi

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Abstract

Objective: Differential diagnosis of androgen excess disorders revealed the occurrence of hyperprolactinemia. However, an elevated level of prolactin (hyperprolactinemia) is a very infrequent cause of hyperandrogenemia in clinical practice. This study aimed to investigate the presence of hyperandrogenism/hyperandrogenemia in women with prolactinoma before and after treatment with cabergoline. **Material and Methods:** Twenty women diagnosed with prolactinoma in the recent past and 15 healthy women between the ages of 18 to 50 were enrolled in the study. Patients were evaluated at the baseline and after six months of cabergoline treatment. Patients were carefully noted for any signs and symptoms of hyperandrogenemia and concentration of androgen in blood. Further, adrenocorticotropin stimulation test was performed to analyze cortisol, dehydroepiandrosterone sulfate (DHEAS), androstenedione, 11-deoxycortisol (11-S), and 17-hydroxyprogesterone (17-OHP) responses. **Results:** A significantly higher level of prolactin compared to the control group was seen in prolactinoma patients, which reverted to normal levels after cabergoline treatment. Estradiol (E2) concentration was lower in patients with prolactinoma than control group and it did not show a significant increase after being treated with cabergoline. Patients with prolactinoma exhibited decreased sex hormone-binding globulin (SHBG) concentration in blood, which also increased significantly after the treatment. The levels of basal androstenedione, DHEAS, 17-OH progesterone, 11-S, and cortisol were found to be similar between the two groups. Basal and stimulated DHEAS and androstenedione levels decreased significantly after cabergoline treatment in prolactinoma patients. The presence of acne, hirsutism, and androgenic alopecia were similar in both groups. Pelvic ultrasonography revealed polycystic ovary (PCO) in nine patients with prolactinoma, which was significantly more frequent than in the control group. Among the 9 PCO patients, normal ovarian morphology was restored in three patients after the treatment. **Conclusion:** From the data, it may be suggested that hyperprolactinemia may not lead to clinically significant hyperandrogenemia and hirsutism. Moreover, the treatment of hyperprolactinemia does not lead to significant improvement in hirsutism score of the patients, if exists.

Keywords: Androgen; hirsutism; hyperandrogenemia; prolactin; prolactinoma

Özet

Amaç: Hiperprolaktinemi, androjen fazlalığı ile seyreden hastalıkların ayırıcı tanılarında araştırılması gereken durumlardandır. Ancak, klinik pratikte hiperprolaktinemi olan hastalarda nadiren hiperandrojenizm görülmektedir. Çalışmamızda, prolaktinoma tanısı almış kadınlarda kabergolin tedavisi öncesi ve sonrası hiperandrojenizmin değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmaya yaş aralığı 18-50 yıl olan, prolaktinoma tanısı konulan 20 kadın hasta ve 15 sağlıklı kontrol dâhil edildi. Hastalar bazal ve 6 aylık kabergolin tedavisinden sonra değerlendirildi. Hiperandrojenizm belirtileri incelendi ve bazal androjen düzeyleri ölçüldü. Adrenokortikotropin stimülasyon testi ile kortizol, dehidroepiandrosteron sülfat (DHEAS) ve androstenedion, 11-deoksikortikol (11-S), 17-hidroksiprogesteron (17-OHP) cevabı değerlendirildi. **Bulgular:** Prolaktinomalı kadın hastalarda kontrol grubuna kıyasla PRL seviyeleri yüksekti ve kabergolin tedavisi ile geriledi. E2 seviyeleri prolaktinoma hastalarında daha düşüktü ve kabergolin sonrası anlamlı bir artış görülmedi. Seks hormon bağlayıcı globulin düzeyleri prolaktinoma hastalarında düşük olmakla beraber, tedavi ile anlamlı derecede yükseldi. Bazal androstenedion, DHEAS, 17-OH progesteron, 11-S ve kortizol düzeyleri 2 grupta benzer bulundu. Prolaktinoma hastalarında, bazal ve uyarılmış DHEAS ve androstenedion seviyeleri, kabergolin tedavisi sonrası anlamlı derece azaldı. Sivilce, hirsutizm ve androjenik alopesi 2 grupta benzer izlendi. Prolaktinomalı 9 kadın hastada kontrol grubuna göre anlamlı olarak daha sık pelvik ultrasonografide polikistik over (PKO) görüldü. Tedaviden sonra PKO olan 9 hastanın 3'ünde normal over morfolojisi görüldü ve 6 hastada hâlâ PKO vardı. **Sonuç:** Çalışmamızda, hiperprolaktineminin klinik olarak anlamlı hiperandrojenizm ve hirsutizme yol açmadığı izlendi. Ayrıca, hirsutizmi olan kadın hastalarda ve hirsutizm skorunda hiperprolaktinemi tedavisi sonrası anlamlı bir iyileşme gözlenmedi.

Anahtar kelimeler: Androjen; hirsutizm; hiperandrojenemi; prolaktin; prolaktinoma

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Introduction

Prolactinomas are the most common form of pituitary adenomas. They account for about 40% of all pituitary adenomas (1). Prolactinoma causes amenorrhea and galactorrhea in premenopausal women, while it causes sexual dysfunction in men. Patients suffering from macroprolactinoma may show signs and symptoms like headache, visual field defects, and pituitary deficiencies. Prolactinomas are found in incidentalomas in few cases (2).

Androgens are the steroid hormones produced by the adrenal cortex, are synthesized in the adrenal glands and ovaries of women. Dehydroepiandrosterone sulfate (DHEAS) is the primary adrenal androgen and is released only in small amounts by the ovaries. The adrenal glands and the ovaries produce androstenedione and testosterone in women. Moreover, a small amount of DHEAS is converted to androstenedione and testosterone in peripheral tissues and adrenal glands (3). Although hypersecretion of DHEAS suggests adrenal hyperandrogenism, they possess little intrinsic androgenic activity. Symptoms of hyperandrogenemia like hirsutism and virilization are caused primally by the more potent androgens such as androstenedione and mainly testosterone (4). In adult women, hyperandrogenism causes hirsutism, acne, androgenetic alopecia, menstrual irregularities, and infertility. It may seldom cause virilization. The most common cause of hyperandrogenism in women is polycystic ovary syndrome (PCOS) (5,6) followed by idiopathic hyperandrogenemia, idiopathic hirsutism, and non-classic congenital adrenal hyperplasia (7,8). Although infrequent, other causes of androgen overproduction that causes hirsutism include androgen-secreting ovarian and adrenal tumors, severe insulin-resistance syndromes, Cushing's syndrome, acromegaly, and hyperprolactinemia. But these diseases appear with more specific and frequent clinical symptoms (9-12).

Although hyperprolactinemia is commonly found in the differential diagnosis of androgen excess disorders, it appears to be a rare cause of hyperandrogenemia in clinical practice (13,14). There are very few studies that investigated the relationship between hyperandrogenemia and hyperprolactinemia. Therefore, the present study aimed to evaluate the existence of hyperandrogenism/hyperandrogenemia before and after treatment with cabergoline in women with prolactinoma.

Material and Methods

It was a prospectively designed study with 20 women with treatment naïve prolactinoma and 15 healthy women of age 18 to 50 years included as controls. Informed consent was obtained from each participant. The patients who used drugs that could increase the prolactin level and had any comorbid conditions were excluded from the study.

The patients were evaluated at the time of diagnosis and after six months of cabergoline treatment. The control group, consisting of healthy individuals, was evaluated only once. The presence of acne, hirsutism and androgenic alopecia was noted in the patients with prolactinoma and healthy controls. Modified Ferriman-Gallwey score (mFG) was exercised for evaluating hirsutism and a score of ≥8 was considered as hirsutism (15).

Basal androgens (total testosterone, androstenedione, and DHEAS), prolactin (PRL), cortisol, thyrotropin (TSH), free thyroxine (fT4), FSH, LH, estradiol (E2) and sex hormone-binding globulin (SHBG) levels were estimated. Free androgen index (FAI) was also calculated from the equation given below

$$\text{Free androgen index (FAI)} = \frac{\text{Total testosterone (nmol/L)}* 100}{\text{SHBG (nmol/L)}}$$

The adrenocorticotropin (ACTH) stimulation test was performed in both groups. A single bolus of 250 µg synthetic ACTH was administered intravenously (Synacthenâ 0.25 mg, Novartis, Nurnberg, Germany). The test was performed in the morning, during the follicular phase of menstruation in patients with a regular cycle. Patients with oligo/amenorrhea, ovulation was excluded by low progesterone levels. Cortisol, DHEAS, androstenedione, 11-deoxycortisol (11-S), and 17-hydroxyprogesterone (17-OHP) levels were measured at 0, 30, and 60 min after the ACTH administration.

Electrochemiluminescence and chemiluminescence methods were used for estimating the hormone concentration. Serum prolactin (PRL), cortisol, total testosterone, DHEAS, SHBG, thyrotropin (TSH), free thyroxine (fT4), FSH, LH, and estradiol (E2) levels were measured by the electrochemiluminescence immunoassay (Cobas® 8000, Roche). IGF–1 and androstenedione levels were determined by chemiluminescence technique (Immulite 2000 XPi, Siemens). Serum 17-OHP level was measured by radioimmunoassay, while liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to measure 11-S concentration.

Pelvic ultrasonography was performed to detect the polycystic ovaries (PCO) and to evaluate their morphology.

Statistical analysis was performed by using SPSS version 21.0. The data were presented as mean±standard deviation. All data were subjected to the Shapiro-Wilk test, which determines the normality of the data. A chi-square test was used for testing relationships between categorical variables. Student's t-test or Mann-Whitney U test was used for comparing the results of both the groups, wherever appropriate. The value of $p<0.05$ was considered statistically significant. The area under the curve (AUC) was calculated following the trapezoid formula. Pearson's correlation coefficient was used to calculate the association between two continuous variables.

Results

The mean age of the patients with prolactinoma and the control group showed similar results (26.9±7.4 and 26.6±4.5, respectively). Two prolactinoma patients had acne, and three of them had hirsutism that persisted after cabergoline treatment (Table 1). The patients with prolactinoma showed higher PRL levels than the control group that were restored to normal values after cabergoline treatment. The E2 levels were lower in the patients with prolactinoma, which did not increase significantly after the treatment (Table 2). SHBG levels were also found to be reduced in patients with prolactinoma, which increased significantly after the treatment. A negative correlation was detected between SHBG, and total testosterone and DHEAS levels (R=-0.58 P=0.023, R=-0.53 P=0.049, respectively). FAI was found slightly higher in patients with prolactinoma that was decreased after treatment; however, the change in data was statistically insignificant. Although the data revealed a positive correlation between PRL levels and total testosterone (R=+0.52 P=0.026), there was no correlation between PRL and FAI, androstenedione, DHEAS, 17-OH progesterone, 11-S levels.

Basal androgen and cortisol levels and responses to ACTH stimulation test are summarized in Table 3. Basal androstenedione, DHEAS, 17-OH progesterone, 11-S, and cortisol levels were found to be similar in both the groups. In patients with prolactinoma, the basal and stimulated DHEAS and androstenedione levels decreased significantly in the cabergoline treated group. Although insignificant, FAI was decreased in prolactinoma patients after cabergoline treatment.

Pelvic USG revealed PCO in nine patients with prolactinoma that was significantly more frequent than in the control group (n:0) (P=0.004). After treatment, normal ovarian morphology was restored in 3 out of 9 PCO patients.

Discussion

Women with hyperprolactinemia have been reported to have hyperandrogenemia and/or hirsutism. However, there are very few studies that investigated the relationship between hyperprolactinemia and androgen excess disorders. In clinical practice, hyperandrogenism and hirsutism are infrequently found in patients with hyperprolactinemia. In this study, prolactinoma was not found to be associated with hyperandrogenemia. Although treatment with cabergoline after six months led to a significant decrease in the basal and ACTH stimulated DHEAS levels but during the initial diagnosis, the patients showed DHEAS levels similar to healthy women.

A study by Glasow et al. showed the presence of PRL receptor using polymerase chain reaction (PCR) and immunohistochemical techniques in the human adrenal gland and adrenal primary cell cultures. PRL receptor was observed in all three zones of the adrenal cortex and marginally in the medulla. The concentrations of cortisol, aldosterone,

Table 1. Clinical features and body composition analysis of the patients with prolactinoma and the control group.

	Patients at baseline (n=20)	Control (n=15)	p_1	Patients after treatment (n:20)	p_2
Age (years)	26.9±7.4	26.6±4.5	0.409		
Acne	2	1	0.610	2	1,000
Androgenic alopecia	0	0	1,000	0	1,000
Hirsutism	3 (%15)	0	0.224	3 (%15)	1,000
Ferriman Gallwey score (median min-max)	4.95 (0-34)	3.0 (0-7)	0.580	4.10 (0-30)	0.115
Height (cm)	161.0±6.4	162.2±6.0	0.595		
Weight (kg)	65.1±14.5	64.6±11.8	0.899	61.9±18.1	0.182
BMI (kg/m^2)	25.1±5.6	4.7±5.0	0.800	25.0±5.8	0.556
Waist circumference (cm)	80.7±11.6	80.5±9.4	0.953	81.1±12	0.575
Body fat percentage (%)	27.8±7.3	29.2±7.0	0.583	28±7.8	0.873
Body fat mass (kg)	19 ±8.9	19.6±8.6	0.857	18.9±8.5	0.994

p_1: p-value for the comparison of the control group and patients with prolactinoma before the treatment, p_2: p-value for the comparison of before and after the treatment of patients.

Table 2. Hormone levels of the patients with prolactinoma and the control group.

	Patients at baseline (n=20)	Control (n=15)	p_1	Patients after treatment (n:20)	p_2
IGF1 (ng/mL)	185.3±67.7	194.4±81.8	0.671	169±45.3	0.272
TSH (µIU/mL)	2.43±1.5	1.84±0.65	0.164	2.69±1.6	0.330
sT4 (ng/dL)	1.2±0.1	1.2±0.1	0.824	1.18±0.1	0.242
PRL (ng/mL)	209±155	21.3±8.4	**<0.001***	15.9±15.5	**<0.001***
FSH (mIU/mL)	5.95±2.3	6.07±1.8	0.866	7.04±2.7	0.156
LH (mIU/mL)	8.06±4.76	8.0±6.0	0.982	6.52±1.9	0.244
E2 (pg/mL)	44.9±34.4	105.9±113.7	**0.034***	49.4±40.6	0.724
TT (ng/dL)	37.9±23.5	41.2±24	0.705	30.1±17.8	0.238
FAI	4.1±3.7	2.9±2.8	0.494	2.1±1.5	0.064
SHBG (nmol/L)	45±23	72±47	0.059	59±24	**0.001***

p_1: P-value for the comparison of the control and patients with prolactinoma at baseline, p_2: P-value for the comparison of patients with prolactinoma at baseline and after treatment. TT: Total testosterone; FAI: Free androgen index.

Table 3. Androgen and cortisol levels of the patients with prolactinoma and the control group.

Hormone	Patients at baseline (n=20)	Control (n=15)	p_1	Patients after treatment (n:20)	p_2
17-OHP (basal) (ng/mL)	1.18±0.83	0.93±0.65	0.426	0.93±0.47	0.180
17-OHP (peak) (ng/mL)	2.76±1.96	1.97±0.57	0.169	2.55±1.83	0.192
AUC (17-OHP response to ACTH)	126.6±93,6	94.2±24.2	0.271	117±77.4	0.280
11-S (basal) (ng/mL)	2.46±1.6	2.19±1.17	0.639	1.99±1.1	0.188
11-S (peak) (ng/mL)	4.28±1.4	4.09±1.43	0.751	3.93±1.6	0.294
AUC (11-S response to ACTH)	190.9±76.3	205±69.1	0.574	188.3±85.9	0.822
Cortisol (basal) (μg/dL)	12.1±4.3	11.8±4.9	0.853	10.8±2.9	0.128
Cortisol (peak) (μg/dL)	25.6±4.6	25.2±3.65	0.801	23.7±3.2	**0.033***
AUC (cortisol response to ACTH)	1231±206	1224±176	0.918	1133±154	**0.030***
DHEAS (basal) (μg/dL)	317±162	293±180	0.886	208±106	**0.003***
DHEAS (peak) (μg/dL)	310±176	310±189	0.899	201.7±111.2	**0.002***
AUC (DHEAS response to ACTH)	18566±9830	17857±10753	0.845	12320±6542	**0.004***
Androstenedione (basal) (ng/mL)	2.7±1.3	2.5±1	0.586	2.1±0.9	**0.048***
Androstenedione (peak) (ng/mL)	4.54±1.97	3.6±1.25	0.140	3.32±1.28	**0.005***
AUC (androstenedione response to ACTH)	229±92	194.1±64.2	0.230	175±73	**0.009***

p_1: P-value for the comparison of the control and patients with prolactinoma at baseline, p_2: P-value for the comparison of the patients with prolactinoma at baseline and after treatment;
AUC: Area under the curve.

and DHEA were found to be enhanced after PRL stimulation in cell supernatant (16).

Kim et al. studied basal androgen levels in 20 hyperprolactinemic women and 7 control subjects. The total testosterone and DHEAS concentrations were similar in both groups. However, the free testosterone level was elevated and the E_2 level was reduced in patients with hyperprolactinemia than the control group (17). Another study reported higher serum DHEAS concentration (basal and after ACTH stimulation) in eight hyperprolactinemic women than the control group. Androstenedione levels were found similar in both groups (18). In the present study, free androgen index and total testosterone levels were similar in the two groups, whereas prolactinoma patients had reduced E_2 and SHBG concentrations. 17-OHP, 11-S, DHEAS, and androstenedione responses to ACTH stimulation were also comparable in patients with prolactinoma and healthy controls.

After cabergoline treatment, the patients were found to have significantly decreased DHEAS response to ACTH stimulation as previously shown (18). Another study by Moria et al. comprising of 122 medically and 26 surgically treated patients with prolactinoma, reported a decrease in DHEAS levels after treatment (19). However, the study did not have a control group and the effects of hyperprolactinemia could not be evaluated at baseline. In the present study, SHBG concentration was found to be increased and the stimulated androstenedione level was found to be decreased significantly in the treated patients. A negative correlation was observed between SHBG and androgen levels. It may be inferred from this situation that hypogonadism due to hyperprolactinemia leads to a decrease in E_2 and SHBG levels, but after treatment, SHBG concentration increased, which may be due to the

decline in androgen levels by cabergoline treatment. A positive correlation was identified between total testosterone and PRL levels as discussed in published reports (20). However, the concentration of total testosterone did not decrease after treatment in the patient group.

In the present study, the patients were evaluated for hyperandrogenism symptoms which include hirsutism, acne, and androgenic alopecia. Although hirsutism was more frequent in patients with prolactinoma, it was statistically nonsignificant and the mFG scores were found similar between the groups. Hagag et al. investigated 80 hirsute and hyperprolactinemic women with prolactinoma, neuroleptic treatment, and idiopathic hyperprolactinemia. In all women, the mFG score, Leed acne score, DHEAS, free testosterone, and androstenedione levels decreased after the treatment with a dopamine agonist drug, which was carried out for 11±1 months (20). However, the study group taken into consideration was very heterogenous and the study also included the cases of drug-induced hyperprolactinemia. It can be inferred that antipsychotic drugs may directly interfere with androgen levels (21-23). In the present study, only a homogeneous group of patients with hyperprolactinemia due to prolactinoma was taken into account. Although DHEAS and androstenedione levels decreased after the treatment as reported, the basal levels of androgens in patient and control groups were comparable in the present study. Also, no significant change was observed after the treatment in the mFG score. DHEAS is known to be a weak androgen, and testosterone is more likely to be responsible for hyperandrogenism symptoms (24). The reduction of DHEAS in patients after treatment may be due to restitution of prolactin levels or a direct effect of cabergoline or both.

For the diagnosis of PCOS, hyperprolactinemia is required to be ruled out. On the other hand, polycystic ovarian morphologly may be seen in 20% of women in the reproductive age group and 5% of them have PCOS (25). In the literature, a few studies and case reports indicates a close association between PCOS and prolactinoma, but there is no prospective study evaluating ovarian morphology in patients with prolactinoma (26,27). In the present study, an increased prevalence of PCO in patients was seen with prolactinoma. After treatment, the ovarian morphology was restored to normal in three of the nine PCO patients.

A relatively limited number of patients with prolactinoma and short follow-up time are the limitations of the present study.

The data, from the above study, suggest that hyperprolactinemia may not lead to clinically meaningful hyperandrogenemia and hirsutism. Moreover, the treatment of hyperprolactinemia does not lead to significant improvement in the hirsutism score of the patients, if exists. A well-known feature of hyperandrogenic disorders is menstrual dysfunction. Hyperprolactinemia should be considered in the differential diagnosis of menstrual disturbances whether associated with hirsutism or not. However, in accordance with the data evaluated in the present study and the published reports mentioned above, it may be suggested that hyperprolactinemia is not a cause of hyperandrogenism/hirsutism per se.

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Ethical Approval

The study was carried out according to the ethical standards of institutional research committee (Erciyes Üniversitesi Etik kurulu Karar no:2016/447 Tarih: 29/07/2016).

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific

and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Kürşad Ünlühızarcı; Design: Züleyha Karaca; Control/Supervision: Züleyha Karaca; Data Collection and/or Processing: Mehmet Çağrı Ünal; Analysis and/or Interpretation: Züleyha Karaca; Literature Review: Kürşad Ünlühızarcı; Writing the Article: Mehmet Çağrı Ünal; Critical Review: Züleyha Karaca; References and Fundings: Fahrettin Keleştemur; Materials: Fahrettin Keleştemur.

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