Research Article

Retrospective analyses of clinical and laboratory features of 646 patients with prolactinoma in Turkey

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Abstract

Background: Prolactinomas are the most frequently occurring pituitary adenomas and consist of nearly 40% of all pituitary adenomas. Their prevalence varies from approximately 60 to 100 inhabitants per million.

Objectives: This study aimed to determine demographic and clinical features of patients with prolactinoma. In addition, it targeted to determine success percentage of medical therapy and frequency of dopamine agonist (DA) resistance.

Materials and Methods: Records of 646 patients who were admitted to Endocrinology and Metabolism Disease department of two hospitals in Turkey between 2007 and 2014 were evaluated retrospectively. Data of the study were obtained from file records for 53% patients and ICD-10 diagnosis code of electronic database of the hospital in 47% of patients.

Results: Of patients who received medical therapy, 91.7% (n = 394) had received cabergoline (CAB) and 8.6% (n = 55) had received bromocriptine (BMC). While normalization rate of prolactin was 92.7% with medical therapy, size of the adenoma completely regressed in 59.7% patients. Size of the adenoma decreased more than 50% in 56% patients. Resistance was detected against DA drugs in 6.9% patients. DA resistance found in 3.9% of patients with microprolactinoma and 27% of patients with macroprolactinoma.

Conclusion: Success percentage of CAB therapy was found greater than BMC therapy in patients with microprolactinoma, which was in line with the literature. And, frequency of DA resistance was found to be lower in patients with microprolactinoma and greater in patients with macroprolactinoma than that reported in the literature.

KEYWORDS: Dopamine agonist resistance, efficacy of dopamine agonist treatment, Prolactinoma

Introduction

Prolactinomas are the most frequent pituitary adenomas and consist of approximately 40% of all pituitary adenomas. Their prevalence varies from approximately 60 to 100 inhabitants per million.[1] The most incidence rate was found in women between 25 and 34 years of age.[2–4] An explanation for this higher prevalence of prolactinomas in premenopausal women is the higher diagnosing rate of hyperprolactinemia in women of reproductive age because it appears with symptoms such as oligomenorrhea, amenorrhea, and/or infertility. Unlike this, symptoms of the disease are more subclinical, except when the macroadenoma exists; it may cause headache and visual field defects in male patients.[1–4]

Hyperprolactinemia frequently causes hypogonadotropic hypogonadism in both men and women due to inhibitory effect of increased prolactin concentrations on hypothalamic gonadotropin-releasing hormone (GnRH) release. Also, hyperprolactinemia may cause anovulatory cycles due to

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inhibition of aromatase activity in granulosa cells and hyperandrogenemia.[5,6] Furthermore, prolactin (PRL) can cause hyperandrogenemia via increase to adrenal steroidogenesis.[7]

The Endocrine Society conducted a systematic review of the literature for evaluating the treatment effects of dopamine agonists (DAs) in patients with prolactinoma.[8] Regarding to the review, the mean percentage of the patients with improved results is the following: decline in tumor size (62%; 20%–100%) and normalization of PRL levels (68%; 40%–100%). These evidences were also obtained from observational studies.[8]

Standard doses of DAs generally provide normalization of PRL levels and a decline in tumor size in patients with prolactinomas. But some patients do not respond.[9] DA resistance is diagnosed as failure to achieve a normal PRL level on maximally tolerated doses of DA and a failure to achieve a 50% reduction in tumor size.[2] The causes of DA resistance are not exactly understood. Decreased number of D2 receptors expressed has been found in resistant prolactinomas.[10–12] The frequency of DA resistance differs between type of DAs, macroprolactinomas or microprolactinomas. DA resistance with regard to normalization of PRL levels and tumor shrinkage may be seen in 25%–50% patients on bromocriptine (BMC), and in 5%–15% taking cabergoline (CAB) therapy.[13] When DA resistance is diagnosed, doses of DA to increase or to switch to another DA therapy or transsphenoidal surgery can be considered in patients with prolactinoma.[14] In patients who fail surgical treatment or who had aggressive or malignant tumor, radiation therapy can be given.[15]

Materials and Methods

The aim of this study was to evaluate patients with prolactinoma retrospectively who attended to Endocrinology and Metabolism Department of two hospitals in Turkey between 2007 and 2014. Institutional review board approval for the study was obtained from ethics committee and patients were asked to sign an informed consent before they were enrolled.

Study Groups

Our study population consisted of patients who were admitted to Endocrinology and Metabolism outpatient clinics of two hospitals in which 168,000 patients are examined yearly. Data of 646 prolactinoma patients who were admitted between 2007 and 2014 were reached. Commonly, patients were referred due to menstrual irregularities or erectile dysfunction and were later diagnosed with prolactinoma after diagnostic testing. Data of the study were obtained from file records in 53% patients and International Classification of Diseases 10 (ICD-10) diagnosis code of electronic database of the hospital in 47% patients.

Systemic inquires of patients were recorded with regard to menstrual disorders, erectile dysfunction, galactorrhea, hirsutism, infertility, headache, and visual disorders. Body weight (kg) and height (cm) of the patients were recorded on admission and body mass index (BMI; kg/m^2) was calculated.

Patients with prolactinoma were divided into two groups, as eugonadic and hypogonadic prolactinoma.[16,5] Those with the levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) below the range (<2–10 mIU/ml) necessary to stimulate follicle development and hence the low levels of E2 (<30 pg/ml) were considered as having hypogonadic prolactinoma, and those with estrogen levels of >30 pg/ml and normal FSH and LH values were regarded as having eugonadic prolactinoma.[16]

Adenomas <1 cm on hypophysis MRI were defined as microprolactinoma and ≥1cm were defined as macroprolactinoma. DA resistance was described as a failure to achieve a normal PRL level on maximally tolerated doses of DA and a failure to achieve a 50% reduction in tumor size.[2]

Biochemical Analyses

Venous blood was drawn for gonadotropin hormone levels on day 3 of follicular phase in patients who had menstrual dysfunction. If the patient had amenorrhea, blood samples were drawn on a random day. Serum FSH (mIU/ml), LH (mIU/ml), TT (ng/ml), PRL (ng/ml), estradiol (E2) (pg/ml), dehydroepiandrosterone sulfate (DHEAS) (μg/dl), and TT (ng/dl) levels were measured by chemiluminescent microparticle immune method (paramagnetic particle, chemiluminescent immunoassay) using a Unicel DxI 800 (Beckman Coulter, Ireland) system immune-analyzer with original reagents. Serum-free testosterone (ng/dl) and androstenedione (ng/ml) levels were determined by radioimmunoassay (RIA) using commercial kits (for FT: BioSource, Nivelles, Belgium; for A: Radim, Roma, Italy). Serum TSH (mIU/ml), free thyroxin (T4) (ng/dl), free triiodothyronine (T3) (pg/ml) levels were assayed with electrochemiluminescence immunoassay (DxI 800; Beckmann Coulter). Reference range for TSH was 0.34–4.25 μIU/ml, for free T3 it was 2.5–3.9 pg/ml, and for free T4 it was 0.61–1.2 ng/dl.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows, version 20). Whether the distributions of continuous variables were normal or not was determined by using Shapiro-Wilk test. Data were expressed as mean±standard deviation for normally distributed continuous variables, whereas continuous variables that did not distribute normally were shown as median (min–max). Percentages were used for categorical variables. Student's *t*-test was used for the normally distributed variables and Mann–Whitney *U*-test was used for the abnormally distributing variables. Pearson's χ^2 or Fisher's exact tests were used to compare differences in rates. A *p*-value of <0.05 was considered indicative of statistical significance.

Results

Of 646 patients, 61 (9.7%) were male and 585 (90.3%) were female. Analysis of all categorical variables including

Table 1: Baseline characteristics of patients with prolactinoma

	Patients (*n*)*	Median value** (IQR)
Age (years)	646	35 (16–79)
BMI (kg/m^2)	631	27.46 (18.47–40.57)
Waist circumference (cm)	631	79.7 (66–129)
PRL (ng/ml)	453	133 (34–5093)
FSH (mIU/ml)	251	7.81 (0–90)
LH (mIU/ml)	250	7.9 (0–81)
E2 (pg/ml)	205	76 (5.43–526)
IGF-1 (ng/ml)	154	176 (11–522)
Androstenedione (mg/dl)	76	0.84 (0.1–4.7)
DHEAS (mcg/dl)	114	207 (85–597)
TT (ng/dl)	112	0.39 (0–3.38)

BMI, body mass index; PRL, prolactin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol; DHEAS, dehydroepiandrostenedione sulfate; TT, total testosterone.
*The number of patients with prolactinomas in whom information was available.

Table 2: Assessment of categorical features of patients with prolactinoma

	Patients with prolactinoma (*n*)*	Median value (%)**
Headache	469	28.6
Sight loss	619	1.9
Galactorrhea	479	32
Amenorrhea	445	26
Oligomenorrhea	470	74
Infertility	382	8.8
Hirsutism	373	8.8
Erectile dysfunction	61	6.3

*The number of patients with prolactinomas in whom information was available.
**The percentage of that subgroup of patients with available information in whom the symptom was present.

demographic features and symptoms on admission are presented in Tables 1 and 2, respectively. Hormone levels and biochemical test results are given in Table 1.

Microadenoma was detected in 74% of patients and macroadenoma was detected in 26%. While mean PRL level was 106 mg/dl for prolactinoma patients with microadenoma, it was 230 mg/dl for prolactinoma patients with macroadenoma.

Although a significant relationship was not observed between PRL level and oligomenorrhea (p = 0.243), amenorrhea (p = 0.378), galactorrhea (p = 0.209), hirsutism (p = 0.785), infertility (p = 0.841), a positive correlation was detected between only tumor volume and PRL levels (p = 0.01, r = 0.381).

Gonadal status was evaluated in 205 of women patients with prolactinoma. Eugonadic hypogonadism was detected in 142 patients and hypogonadotropic hypogonadism was detected in 63 patients. Mean PRL level of eugonadic prolactinoma was 111 ng/ml (46–299), mean PRL level of hypogonadic prolactinoma was 128 ng/ml (41–419), and a statistically significant difference was not detected. Similarly, no difference was found between prolactinoma patients with microadenoma and macroadenoma with regard to gonadal status. No difference was found between androgen hormone levels (DHEAS, TT) of eugonadic and hypogonadic prolactinoma. Amenorrhea, galactorrhea, and headache were observed more frequently in hypogonadotropic hypogonadism patients compared to eugonadic patients (p = 0.039, 0.031, and 0.028).

When medical records of 431 patients were analyzed, it was found that 91.7% (n = 394) patients had received CAB and 8.6% (n = 55) had received BMC. Mean duration of therapy was found to be 2.3 years (0–12).

While normalization rate of PRL level was 92.7% with medical therapy, size of the adenoma completely regressed in 59.7% of patients. Size of the adenoma decreased more than 50% in 56% of patients. Although adenoma completely regressed in 74.4% of patients with microadenoma, this rate was 50% in patients with macroadenoma (p = 0.471). PRL normalization rate was 93.4% in microadenoma patients and 74.2% in macroadenoma patients after treatment (p = 0.002).

In patients receiving CAB, whereas PRL normalization was 93.8%, adenoma regressed completely in 69.6% patients. Size of the adenoma regressed more than 50% in 71% patients. Although PRL normalization rate was 97% in patients receiving BMC, adenoma regressed completely in 50% of patients. Size of the adenoma regressed more than 50% in 29% patients.

The mean age, sex distribution, adenoma size, and PRL levels were similar in CAB and BRC groups (36±0.8 vs 31±1.1, p = 0.375; 90.3% women and 9.8% men vs 92.1% women and 7.9% men, p = 0.979; 136±12 vs 104±8, p = 0.304; 0.43±1.8 vs 0.10±0.14, p = 0.08).

Tumor volume shrinkage for CAB group (36.4±39.7 cm^3) and BMC group (25±45.1 cm^3) were not significantly different in all patients with prolactinoma (p = 0.091). CAB treatment was observed to be superior to BMC treatment for normalization of PRL level (96% vs 71%) and with regard to complete remission (69% vs 36%) (p = 0.011 and 0.003, respectively).

While success percentage was 76.3% for PRL normalization after CAB treatment in macroadenoma patients, that of complete remission was 52.5%. Our study did not include patients with macroprolactinoma who were on BMC treatment; therefore, CAB and BMC treatments could not be compared in patients with macroprolactinoma.

Resistance to medical therapy was detected in 6.9% patients. Resistance was detected in 3.9% of microadenoma patients and 27% of macroadenoma patients, and the difference was statistically significant (p = 0.014). Resistance to therapy was found to be significantly lower in CAB group (5.8%) than that in BMC group (3.6%) (p = 0.02).

Hypophysis adenomectomy with TN/TS way was performed in 30 patients who were detected to be resistant to medical therapy, and thereafter conventional radiotherapy

was applied in 7 patients. Malignancy was not detected in any of the operated patients with prolactinoma.

Discussion

The prevalence of prolactinomas ranges from 6 to 10 per 100,000 individuals to approximately 50 per 100,000[17,18] individuals. Recently, higher prevalence rates of 44–62 per 100,000 individuals have been reported.[17,18] One study showed the mean prevalence of 1.607 patients with hyperprolactinemia, which was approximately 10 per 100,000 in men and approximately 30 per 100,000 in women, and a peak prevalence for women aged 25–34 years.[19] In our study, median age of the patients who were admitted with hyperprolactinemia symptoms was 34 years for women and 43 for men.

The most common symptoms of hyperprolactinemia in premenopausal patients with prolactinoma are oligomenorrhea/secondary amenorrhea and galactorrhea.[20,21] One study showed that oligomenorrhea and secondary amenorrhea in patients with prolactinoma occurred in 40.33% of patients.[22] Similarly, our study revealed that the most symptoms of hyperprolactinemia were oligomenorrhea, secondary amenorrhea, and galactorrhea. Several studies showed that serum PRL levels generally parallel adenoma size.[22–24] Likewise, we have noted significant correlation between PRL levels and adenoma size.

Prolactinoma may be presented with different PRL levels. PRL levels are generally higher than 250 μg/l in the most patients with prolactinoma.[23,24] And, serum PRL levels in patients with macroadenomas (greater than 250 μg/l) were usually higher than those in patients with microadenomas.[23,24] In one study that included 46 men patients with prolactinoma, serum PRL levels were found to be elevated at a mean 99 μg/l (range 16–385) in 12 patients with microadenomas and a mean of 1415 μg/l (range 387–67.900) in 34 patients with macroprolactinomas.[25] In our study, while mean PRL level was 106 ng/ml for prolactinoma patients with microadenoma, it was 230 ng/ml for prolactinoma patients with macroadenoma.

The increase in PRL levels leads to hypoestrogenism by inhibiting GnRH secretion and LH/FSH release.[26] Menstrual cycle irregularities in patients with prolactinoma can be seen without any change in the levels of FSH, LH, and E2, which were termed as eugonadic patients with prolactinoma. Contrary to this,[5] a study and the present study did not show a negative correlation between PRL levels and FSH and LH levels.[26] Also, the present study did not observe PRL level and adenoma size differences between hypogonadic and eugonadic patients with prolactinoma. But, occurrences of secondary amenorrhea, galactorrhea, and headache were higher in hypogonadic than those in eugonadic patients with prolactinoma.

Hyperprolactinemia may lead to anovulatory cycles with mechanisms different from secondary hypogonadism. When the studies were conducted on the causes of menstrual dysfunction in patients with prolactinoma, a relationship between hyperandrogenism and hyperprolactinemia was found.[26–30] But, the present study did not indicate relationship between DHEAS, total testosterone (TT), AS, and PRL levels.

Several studies have shown the efficiency of CAB therapy in normalizing PRL levels, and in reduction tumor size, especially in microprolactinomas.[31–33] They showed that normalization of PRL levels was observed in 75%–90% of patients with microprolactinomas and macroprolactinomas and a mean decrease of 72%–92% in tumor volume was.[31–33] In our study, although the influence of CAB therapy on prolactinoma patients with microadenoma and macroadenoma was similar (96% vs 69%), that on complete remission of the tumor was seen to be less in patients with macroadenoma (76% vs 52%).

One study indicated that the percentage of disappearance of tumor was 53% and 28% in patients with microprolactinomas and macroprolactinomas, respectively.[34] In our study, the tumor disappeared in 74.4% of patients with microadenoma and in 50% of patients with macroadenoma.

Some studies showed the percentage of normalizing PRL levels and reducing tumor volume in 60%–80% of patients with microprolactinomas for BMC therapy.[32,35] Also, BMC was found to be effective in only 50%–70% patients with macroprolactinomas.[36,37] In our study, although BMC treatment given to microprolactinoma patients normalized PRL value in 71% patients, tumor disappeared in only 36% patients.

It is not understood why CAB is more effective than BMC; one reason may be that incidence of side effects is higher with BMC.[5] But randomized clinical trials have not yet compared tumor shrinkage effects of different DAs head to head. Anyway, results of various studies showed that BMC reduced tumor size by approximately 50% in two thirds of patients with prolactinoma, compared with a 90% reduction with CAB.[36] One meta-analysis, which included mostly cases series and/or retrospective studies, indicated that normalization of serum PRL levels was achieved in CAB group (RR 0.67 [CI 95% 0.57–0.80]) than BMC group (RR 0.74 [CI 95% 0.67–0.83]).[37]

D2 receptor expression level is one of the causes of DA resistance; this rate may vary in gene pool of every country.[10,11] There are approximately 5%–10% patients with prolactinoma resistant to CAB therapy and 25%–50% with prolactinoma resistant to BMC in the literature.[13,34–41] Similarly, our study showed that prolactinoma resistance to CAB therapy (5.8%) was lower than that to BMC therapy (31.6%) in all patients with prolactinoma.

Microadenomas are less resistant to DAs than macroadenomas in patients with prolactinoma. Ten percent of patients with microprolactinomas and 18% of patients with macroprolactinomas do not succeed in normalizing PRL levels on CAB therapy.[41,32] Furthermore, men were more prone to DA resistance than women.[42] In our study, although resistance to medical therapy was lower in patients with microadenoma (3.9%), this rate was found higher in patients with macroadenoma (27%).

The prevalence of pituitary carcinomas is very low,[43] just 140 cases with pituitary carcinomas have been reported until now.[43–45] Malignant prolactinoma was not detected in our prolactinoma cases.

Study Limitation

Comparison of success percentage between CAB and BMC therapies could be done for only patients with microprolactinoma as no patients with macroprolactinoma had received BMC therapy in our study.

Conclusion

Success percentage of CAB therapy was higher than that of BMC therapy in patients with microprolactinoma, which is consistent with that reported in the literature. And, frequency of DA resistance was found to be lower in patients with microprolactinoma and higher in patients with macroprolactinoma than that reported in the literature.

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