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Evaluation of the gender effect in operated prolactinomas

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ABSTRACT

Objectives: To investigate the differences between the characteristics of disease presentation and treatment outcomes on the basis of gender in patients with operated prolactinoma.

Methods: Prolactinoma patients who underwent endoscopic transsphenoidal surgery at Istanbul University-Cerrahpasa, Neurosurgery clinics between 2013-2023 were included in this study. Surgical indications, secondary treatments, clinical, demographic, biochemical, radiological findings, and pathological data were analyzed. Data were compared between the gender groups.

Results: Thirty-two men and 28 women were included in the study. The mean age of the men was 44 years and that of the women was 29 years. While men were more likely to have decreased libido, women were more likely to have menstrual irregularities ($p < 0.001$). The tumor was larger in men ($p = 0.001$), presenting with a more frequent suprasellar invasion ($p = 0.001$) and cavernous sinus invasion ($p < 0.001$). Pituitary hormone deficiency ($p < 0.001$) and visual field defects ($p < 0.001$) occurred more frequently in men.

Conclusions: Male prolactinoma patients tend to have more invasive and larger tumors. Men are less likely than women to go into remission with surgery. This difference in presentation may be due to indistinct symptoms in male patients and late diagnosis.

Keywords: Prolactinoma, remission, sex, surgery

Prolactinomas are the most common functional pituitary adenomas [1]. Oligomenorrhea and galactorrhea in women, decreased libido and infertility in men are the most common symptoms [2]. Less commonly, the adenoma is discovered incidentally by a neuroimaging result or when looking for symptoms of a pituitary mass effect, such as a visual field defect, followed by a secondary prolactin measurement [3]. Dopamine agonists are recommended as first-line therapy for prolactinomas due to their proven high efficacy [4]. Surgical removal of the adenoma is recommended as second-line therapy but as first-line therapy in selected cases: (i) resistance to dopamine agonists; (ii) presence of intolerance to dopamine agonists; (iii) immediate or progressive neurological deficit; (iv) patient preference [5]. The preferred method for surgical removal of the adenoma is endoscopic transsphenoidal surgery (ETSS) [6].

There is a significant difference in the prevalence of prolactinoma according to gender and age [7].

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While the sex ratio between females and males for prolactinomas is 10:1 between the second and the fifth decade of life, it decreases to 1:1 after that [7]. One explanation for this situation is the increased expression of estrogen receptors in prolactinomas [8]. Previous studies investigated whether this sex selection influences the occurrence of the disease as well as the efficacy of the applied treatments and reported the negative influence of the male sex on surgical outcomes [9,10]. Similarly, in another previous study, we found that male gender was associated with failure in surgical remission in prolactinomas [11]. This study aimed to compare the characteristics of patients with prolactinoma treated with ETSS at a tertiary center by sex and to obtain data that shed light on the reasons for sex selection in this disease.

METHODS

This single-center, retrospective study was conducted at the Pituitary Center of a tertiary care university hospital and approved by the Research Ethics Committee of Istanbul University-Cerrahpasa. Patient data were coded and stored anonymously.

Study Design and Procedure

Patients with prolactinoma who underwent ETSS in the Department of Neurosurgery, Istanbul University-Cerrahpasa, between 2013 and 2023 were studied. Inclusion criteria were (i) a definite pathological diagnosis of prolactinoma; (ii) adult patients. Exclusion criteria were (i) patients who underwent surgery for a sellar mass but who did not have prolactin immunostaining; (ii) patients with positive immunostaining for both prolactin and other hormones (mixed or plurihormonal pituitary adenoma); (iii) medically treated prolactinoma patients; (iv) patients with missing follow-up data.

Demographic data, type and duration of medical treatment, reasons for the decision to operate, prolactin level at presentation, tumor size before surgery, presence of suprasellar extension, presence of cavernous invasion, Hardy and Knosp stages, type of resection during surgery, complications, pathology results, postoperative prolactin level, prolactin level at last visit, postoperative radiotherapy, and ongoing medical treatment after surgery were collected from all participants. In the final analysis, all these data were evaluated by two gender groups.

Statistical Analysis

The statistical analyses in this study were conducted using the Statistical Package for the Social Sciences (SPSS) software, specifically version 21.0. To assess the normality of the data, the Kolmogorov-Smirnov test was employed. Continuous variables were presented as mean ± standard deviation (SD) or medians with interquartile range (IQR) if the data distribution was not normal. For comparing means between groups with normally distributed data, Student's t-tests or analysis of variance (ANOVA) were utilized. In cases where the data did not follow a normal distribution, medians were compared using the Mann-Whitney U test or Kruskal-Wallis test. Correlation coefficients between continuous variables were calculated using Spearman's rank order or Pearson correlation tests. To compare frequencies, Pearson's chi-square test or Fisher's exact test was employed. The significance level was set at $p < 0.05$, and all results were evaluated with a 95% confidence interval.

RESULTS

A total of 60 patients treated surgically for prolactinoma were included in this study. Thirty-two were men and 28 were women. The most common admission symptom in males was decreased libido (75%), and the most common symptom in females was oligomenorrhea (71.4%). The characteristics of patients at preoperative presentation and comparison of tumor pathologies are shown in Table 1. The median age at surgery was 44.3 years in men and 29.1 years in women ($p < 0.001$). Median prolactin levels in men at diagnosis were 919 ng/mL, significantly higher than in women at 127 ng/mL ($p = 0.004$).

Men were found to have significantly larger tumor sizes at surgery ($p = 0.001$), higher suprasellar extension rate ($p = 0.001$), and higher prevalence of cavernous sinus invasion ($p < 0.001$) compared with women. There was no statistically significant difference between the two groups in the distribution of tumors in the micro, macro, and giant adenoma categories ($p = 0.110$). A comparison of the patient's preoperative Modified Hardy-Wilson grades (sellar

Table 1. Comparison of preoperative findings and pathological features

	Male	Female	*p* - value
Age (year), mean (range)	44.3 (18-72)	29.1 (16-58)	**< 0.001**
Prolactin at diagnosis (ng/mL), median [IQR]	919 [455-3829]	127 [75-191]	**0.004**
Preoperative prolactin (ng/mL), median [IQR]	305 [23-700]	100 [49-147]	**0.043**
Maximal tumor diameter (mm), median (range)	27.5 (10-65)	14 (4–61)	**0.001**
Preoperative visual field deficiency, n (%)	24 (75)	4 (14.3)	**< 0.001**
Tumor size category, n (%)			
Micro	1 (3.1)	3 (10.7)	0.110
Macro	24 (75)	24 (85.7)	
Giant	7 (21.9)	1 (3.6)	
Suprasellar extension, n (%)	24 (75)	9 (32.1)	**0.001**
Cavernous sinus invasion, n (%)	26 (81.3)	12 (42.9)	**< 0.001**
Intraoperative adenoma structure, n (%)			
Cystic	7 (21.9)	8 (28.6)	0.551
Hemorrhagic	4 (12.5)	5 (17.9)	
Solid	16 (50)	13 (46.4)	
Mixt	5 (15.6)	2 (7.1)	
Ki -67 labeling index, mean ± SD	2.3 ± 2.1	2.7 ± 1.7	0.464
Sparse granular adenoma structure, n (%)	23 (71.9)	16 (57.1)	0.260

IQR = Interquartile range, SD = Standard deviation

destruction grade), Modified Hardy-Wilson stages (extrasellar expansion stage), and Knosp grades are given in Table 2. The Ki-67 labeling index in pathology reports was, on average, slightly higher for women than for men, 2.70 and 2.26, respectively, but this was not statistically significant ($p = 0.464$).

The assessment regarding pituitary hormone deficiency before surgery is shown in Table 3. The presence of at least one hormone deficiency was significantly more frequent in male than in female patients ($p < 0.001$). Data on patients treated preoperatively with dopamine agonists and the duration and dosage of medical treatments are shown in Table 4. The most common reason for surgery in men was the presence of an immediate/progressive neurologic deficit; in women, the most common reason for surgery was drug resistance (Table 4).

Most patients did not experience postoperative complications. No leakage of cerebrospinal fluid was observed postoperatively in any of the patients. Persistent diabetes insipidus, meningitis, vascular complications, and patient death did not occur. Evaluation of surgical outcomes and follow-up data are shown in Table 5. The gross overall resection rate and surgical remission rates evaluated at the third postoperative month were significantly higher in women ($p = 0.001$). The remission rates evaluated at the last visit were similar in both groups ($p = 0.097$). However, remission with medication was significantly higher in men ($p < 0.001$).

DISCUSSION

In this study, gender differences in prolactinoma presentation, treatment outcomes, and disease progression were investigated. Male patients had higher prolactin levels, larger tumors, more pituitary hormone deficiency, more tumor compression findings, and lower surgical remission rates at diagnosis. Women tended to report at a young age and with irregular menstruation. Men, on the other hand, presented at older ages

Table 2. A comparison of the patients' preoperative Modified Hardy-Wilson grades (sellar destruction grade), modified Hardy-Wilson stages (extrasellar expansion stage), and Knosp grades

	Male	Female	*p* value
Modified Hardy-Wilson grades, n (%)			**< 0.001**
1	0 (0)	5 (17.9)	
2	5 (15.6)	14 (50)	
3	5 (15.6)	4 (14.2)	
4	22 (68.8)	5 (17.9)	
Modified Hardy-Wilson stages, n (%)			**0.001**
A	13 (40.6)	21 (75)	
B	4 (12.5)	3 (10.7)	
C	0 (0)	0 (0)	
D	8 (25)	4 (14.3)	
E	7 (21.9)	0 (0)	
Knosp grades, n (%)			**0.002**
0	5 (15.6)	12 (42.8)	
1	4 (12.5)	8 (28.6)	
2	4 (12.5)	5 (17.9)	
3	7 (21.9)	2 (7.1)	
4	12 (37.5)	1 (3.6)	

and with loss of libido.

Prolactinomas are more common in females [12]. However, there were more male patients in this series. In our center, surgery is performed in selected cases of prolactinoma patients. Immediate/progressive neurological deficits were the most important surgical indication and were significantly higher in male patients. Moreover, in other series, women tended to be 10 years younger at the time of diagnosis [12, 13]. This is also the case in our series. The difference in the frequency of the disease between the sexes might be related to the differences in clinical presentation. The clinical manifestation of hyperprolactinemia in men and women can be explained by the fact that men are more prone to symptoms such as low libido and erectile dysfunction, which are more insidious and often underestimated clinically and/or present later for sociocultural reasons. Therefore, men may seek medical attention much later than when symptoms appear [13]. Our results were also in this direction. Because the most common symptoms in men and women were decreased libido and menstrual irregularities, respec-

Table 3. Evaluation of pituitary hormone deficiency before surgery

	Male	Female	*p* value
At least one pituitary hormone deficiency before surgery, n (%)	29 (90.6)	9 (32.1)	**< 0.001**
Thyroid-stimulating hormone deficiency, n (%)	16 (50)	5 (17.9)	**0.031**
Adrenocorticotropin hormone deficiency, n (%)	11 (34.4)	5 (17.9)	0.290
Gonadotropin hormones deficiency, n (%)	25 (78.1)	4 (14.3)	**< 0.001**
Growth hormone deficiency, n (%)	4 (12.5)	3 (10.7)	0.758

Table 4. Preoperative medical treatment and reasons for the operation

	Male	Female	*p* value
Medical treatment with a preoperative dopamine agonist, n (%)	28 (87.5)	20 (71.4)	0.187
Duration of preoperative medical treatment (months), median [IQR]	3 [1-12]	12 [1-30]	0.057
Preoperative medical treatment maximum dose*, mean ± SD	1.86 ± 1.25	1.6 ± 1.4	0.498
Indications of the operation, n (%)			
Dopamine agonist resistance	11 (34.4)	13 (46.4)	0.047
Dopamine agonist intolerance	5 (15.6)	3 (10.7)	
Patient preference	3 (9.4)	9 (32.2)	
Immediate/progressive neurologic deficit	13 (40.6)	3 (10.7)	

*Maximum DA dose data used are given as equivalent doses in cabergoline (mg/week). IQR = Interquartile range, SD = Standard deviation

tively. As opposed to an actual incidence, women may be thought to be affected more frequently and at an earlier age because of more pronounced clinical signs and symptoms. Previously autopsy studies found that the prevalence of postmortem prolactinomas was similar in men and women [14]. However, these are hypotheses and causality cannot be established with certainty.

We found that men had significantly larger tumors compared with women and therefore more mass effect-related symptoms, such as visual disturbances. In addition, cavernous sinus invasion, suprasellar spread, Hardy and Knosp stages, which are clinical markers of advanced and aggressive tumors, were significantly higher in men. These results are consistent with other series and the literature [10, 15-18]. In general, the differences in tumor size and aggressiveness have been attributed to the fact that the tumor is detected later in men. It has also been argued that differences in tumor biology are a cause. Studies have claimed that male tumors have a higher number of Ki-67 staining, which can be attributed to greater tumor size and aggressiveness [17-19]. However, our results did not differ between males and females in terms of the Ki-67 labeling index.

We observed that the male patients in our population had higher prolactin levels at diagnosis than the female patients. It has been previously shown in the literature that males have shorter symptom duration before surgery, higher preoperative serum prolactin levels, and more drug-resistant diseases [15-18, 20, 21]. In this series, women had tumors resistant to

Table 5. Surgical results and follow-up

	Male	Female	*p* value
Gross total resection, n (%)	11 (34.4)	21 (75)	**0.001**
Postoperative first-week prolactin (ng/mL), median [IQR]	56 [3-421]	9.5 [2.4–27.8]	**0.011**
Last prolactin (ng/mL), median [IQR]	18 [5-86]	17 [9-34]	0.184
Surgical remission, n (%)	11 (34.4)	25 (89.3)	**< 0.001**
Recurrence, n (%)	5 (15.6)	4 (14.3)	0.831
Postoperative secondary treatments, n (%)			
Dopamine agonist, n (%)	27 (84.4)	7 (25)	**< 0.001**
Radiosurgery, n (%)	3 (10.7)	1 (3.6)	0.175
Reoperation, n (%)	4 (12.5)	1 (3.6)	0.244
Remission at last visit, n (%)	27 (84.4)	28 (100)	0.097

IQR = Interquartile range.

dopamine agonist therapy, which was often the reason for surgery. In this case, we can attribute the earlier diagnosis in women to the fact that medical treatment was initiated before the disease was complicated. Therefore, they were less likely to need emergency surgery. And they were more often operated on when medical treatment was tried and did not work.

In our study, there were also differences between the two sexes in terms of surgical outcomes. Men were found to have significantly lower gross resection rates, lower surgical remission rates, and a higher need for continued medical treatment with a dopamine agonist after surgery. These results are consistent with previous reports showing lower remission rates in men than in women [10, 20]. This is because the postoperative remission rate is likely related to tumor size and invasiveness. Microprolactinomas without cavernous sinus invasion have been reported in the literature to have higher remission rates [22].

Limitations

This study has several limitations. Our study was not selected from all patients with prolactinomas but from patients who had surgery for their prolactinomas; this may explain some of the differences in results from previous studies by introducing selection bias. Patients in our tertiary referral center may be more advanced and complicated because patients are more often treated initially in external centers. For the same reason, the number of our patients with microprolactinoma was significantly lower. In addition, the lack of molecular and genetic studies that could explain the differences between the sexes prevents us from making further comments.

CONCLUSION

In this study, we found that male prolactinoma patients who underwent surgical treatment differed significantly from female prolactinoma patients in larger tumor size, higher prolactin levels, higher frequency of suprasellar invasion, and higher frequency of cavernous invasion. Men were less likely than women to have a complete resection at their surgery and to remain in drug-free remission after surgery. In addition, men were more likely to lose libido, while women were most likely to have menstrual irregularities. All of these findings suggest that diagnosis is delayed in men and that outcomes can be improved if an early diagnosis is made. However, further research at the molecular level is needed to understand gender-based differences.

Authors' Contribution

Study Conception: DÖ, AND, NT; Study Design: DÖ, AND, NT; Supervision: NT; Funding: DÖ, AND, NT; Materials: DÖ, AND, NT; Data Collection and/or Processing: DÖ, AND; Statistical Analysis and/or Data Interpretation: DÖ, AND, NT; Literature Review: DÖ, AND, NT; Manuscript Preparation: DÖ, AND, NT and Critical Review: DÖ, AND, NT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

Statement of ethics

The study adhered to the ethical principles for medical research involving human participants described in the World Medical Association's Declaration of Helsinki. The Ethics Committee of Istanbul University-Cerrahpasa approved the study (Approval Number: E-83045809).

Informed consent:

Signed informed consent was obtained from all study participants.

Data statement

The data used and analyzed during the current scoping review are available from the corresponding author upon reasonable request.

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