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Comparison of Male and Female Prolactinoma Patients Requiring Surgical Intervention

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Abstract

Objectives Prolactinomas are the most common functional pituitary adenoma. Symptoms of a prolactinoma stem from hormonal causes (menstrual irregularities, galactorrhea, and reduced libido) or from tumor mass effect (visual changes and headache). Gender differences have been noted in prolactinomas, with males presenting with larger tumors and sequelae of mass effect, while females present commonly with hormonal symptoms. The purpose of this study is to evaluate differences in patient and disease characteristics, and outcomes between male and female prolactinoma patients undergoing surgery.

Design This was a retrospective chart review.

Setting This was done at the tertiary medical center.

Participants The medical records of prolactinomas patients who underwent endoscopic endonasal surgery between March 2008 and August 2016 were reviewed.

Main Outcome Measures Demographic information, tumor characteristics, and treatment characteristics and outcomes were collected. Statistical analysis was performed using chi-squared test or Student's *t*-test as applicable.

Results Seventy-nine patients were identified, 22 males and 57 females. The average age for males was 38 years and for females was 35 years. Males were more likely to present with decreased libido ($p < 0.0001$), whereas females more often presented with galactorrhea ($p < 0.0001$) and menstrual irregularities. Tumor size was larger in males ($p = 0.0044$) with higher likelihood of suprasellar extension ($p = 0.0409$) and cavernous sinus invasion ($p = 0.0026$). Males were more likely to have a subtotal resection rather than gross total resection ($p = 0.0086$) and less likely to have normalization of prolactin levels following surgery ($p = 0.0019$).

Conclusion Male prolactinoma patients tend to have larger tumors with more aggressive features. This may have a role in the differences in outcomes noted in this study.

Keywords

- ▶ pituitary adenomas
- ▶ prolactinoma
- ▶ gender
- ▶ endoscopic

Introduction

Prolactinomas are the most common of all pituitary adenomas, accounting for 51 to 66% of these tumors.¹ Common presenting symptoms include headache, visual impairment, galactorrhea, and effects of hypogonadism including ame-

norrhea, infertility, and erectile dysfunction.² Dopamine-agonist therapy including cabergoline and bromocriptine are the first-line treatments for prolactinomas. However, some patients will require surgical treatment because they are refractory to medical therapy, are intolerant to medication side effects, desire pregnancy, or due to patient

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preference.³ The endoscopic endonasal approach has largely become the standard surgical approach due to magnified and panoramic views, decreased invasiveness, and high rate of successful outcomes.⁴⁻⁶ Previous analyses have reported that up to 93% patients with prolactinomas achieve remission with surgery, with variability due to the extent of invasion and size of the tumor.^{1,7-9}

Studies have noted some gender differences in prolactinomas. Hyperprolactinemia has been shown to be more common among women with the incidence varying with age.¹⁰ However, prolactin levels have been found to be higher in men, which has been attributed to be likely due to the increased frequency of macroadenomas at presentation.¹¹ These findings have not been completely elucidated. Some attribute it to the later onset of vague symptoms resulting in delayed diagnosis, while others to the tumor biology.¹²⁻¹⁵ Men typically present with decreased libido and impotence, whereas women tend to have more clear-cut symptoms including menstrual dysfunction and galactorrhea.^{15,16} Thus far, there have also been conflicting results determining if there is a difference in response to medical treatment in males and females.^{15,17}

Although there are studies looking at these gender differences in prolactinomas, there is limited data evaluating these two cohorts in the setting of surgical management. One recent study evaluating 142 surgical cases of prolactinoma showed that gender was an independent factor in predicting persistent disease following surgery.⁷ The aim of this study is to compare males and females with prolactinomas that had undergone transnasal transsphenoidal endoscopic surgery for management of their prolactinomas at a single institution, comparing their characteristics at presentation, response to medical therapy, and surgical outcomes.

Methods

Retrospective review was performed on all patients who underwent transnasal transsphenoidal endoscopic resection of prolactinoma from March 2008 to June 2016. Data were extracted from patient charts including demographics, type of medical therapy, length of medical therapy trial, response to medical therapy, reasons for proceeding to surgery, presenting symptoms, presenting prolactin level, tumor size at surgery, presence of suprasellar extension, presence of cavernous sinus invasion, type of resection achieved during surgery, presence of intraoperative cerebrospinal fluid (CSF) leak, complications, postoperative prolactin level at 2 months, length of stay, postoperative radiation therapy, and continued medical therapy following surgery. Statistical analysis was performed using Fisher's exact test or chi-square test for categorical variables, and two-tailed *t*-tests for continuous variables. Assumption of equal or unequal variance was determined by performing the *F*-test of the equality of variances and performed as indicated. Significance was set at a *p*-value of less than 0.05.

Results

In total, there were 79 patients who underwent surgical treatment for prolactinoma included in this study. Twenty-

two patients were male and 57 patients were female. Preoperative patient characteristics are shown in ►**Table 1**. Average age at the time of surgery was 38 years for males and 35 years for females ($p = 0.2932$). Males tend to have higher frequency of atypical adenoma, but this was not statistically significant ($p = 0.0750$). Presenting symptoms differed between males and females. Males tend to present with more decreased libido ($p < 0.0001$) and females tend to present more often with galactorrhea ($p < 0.0001$). The most common presenting symptom for males was decreased libido (50%) and the most common presenting symptom for females was menstrual irregularities (77.2%). Males were found to have higher average prolactin levels at diagnosis at 2,281 ng/mL compared with females with 532.9 ng/mL, but this was not statistically significant. Males were found to have significantly larger tumor size at surgery ($p = 0.0044$), higher rate of suprasellar extension ($p = 0.0409$), and higher prevalence of cavernous sinus invasion compared with females ($p = 0.0026$). The distribution of tumors into categories of micro-, macro-, and giant adenomas was also significant ($p = 0.0062$), with note that there were no giant adenomas in the female group. The Ki-67 labeling index on final pathology reports was slightly higher on average for males than females, 4.77 and 3.52, respectively, but this was not statistically significant.

The summary of the medical therapy received by the patient population is presented in ►**Table 2**. No significant differences were noted between males and females regarding percentage of patients trialed on medical therapy with a dopamine agonist prior to surgery, prolactin level response to medical therapy, tumor size response to medical therapy, and length of medical therapy. For males, the most common reasons for pursuing surgery were partial/no response to dopamine-agonist therapy and persistent/worsening symptoms. For females, the most common reasons for pursuing surgery were partial or no response to dopamine-agonist therapy followed by intolerance of side effects of medical therapy.

The operative outcomes are presented in ►**Table 3**. Female patients were found to have significantly higher rates of gross total resection ($p = 0.0086$) and normalization of serum prolactin levels 2 months following surgery ($p = 0.0016$) compared with male patients. There was no significant difference between the two genders in regard to complications from surgery, presence of an intraoperative CSF leak, length of stay, or undergoing postoperative radiotherapy. Male patients tend to require continued medical therapy with dopamine-agonist therapy following surgery compared with female patients, and this difference approached significance ($p = 0.0536$).

Subgroup analysis of the gender groups with respect to size of tumor in categories of micro-, macro-, and giant adenomas was performed (►**Table 4**) showing that in males, there was a statistically significant increase in prolactin level with size (Spearman rho = 0.6184, $p = 0.0022$) and a near significant increase in Ki-67 labeling index with size (Spearman rho = 0.4021, $p = 0.0636$). In females, however, there were no significant increases in prolactin level with size (Spearman rho = 0.2267, $p = 0.0899$) and Ki-67 labeling

Table 1 Preoperative patient and tumor characteristics

	Males (n = 22)	Females (n = 57)	p-Value
Age at surgery (y)	38 (SD 15.56)	35 (SD 9.28)	0.2932
Hormone secretion			
PRL only	19	46	0.7461
PRL + other	3	11	
Pituitary adenoma grade			
Typical adenoma	20	57	0.0750
Atypical adenoma	2	0	
Presenting symptoms			
Decreased libido	11 (50%)	3 (5.3%)	<0.0001
Gynecomastia	9 (40.9%)	N/A	
Menstrual irregularities	N/A	44 (77.2%)	
Galactorrhea	2 (9.1%)	35 (61.4%)	<0.0001
Headache	9 (40.9%)	17 (29.8%)	0.4254
Visual disturbance	6 (27.3%)	7 (12.3%)	0.1723
PRL level at diagnosis (ng/mL)	2,281.0 (SD 4,715.82)	532.9 (SD 1,213.87)	0.1000
Tumor size at surgery (mm)	18.9 (SD 11.73)	10.7 (SD 5.37)	0.0044
Tumor size category			
Micro	7	34	0.0062
Macro	12	23	
Giant	3	0	
Suprasellar extension			
Yes	9	10	0.0409
No	13	47	
Cavernous sinus invasion			
None	13	52	0.0026
Unilateral	8	5	
Bilateral	1	0	
K _i -67 labeling index (average)	4.77	3.52	0.4240

Abbreviations: N/A, not available; PRL, prolactin; SD, standard deviation.

index with size (Spearman rho = 0.1164, $p = 0.3886$). In both genders, the rate of subtotal resection increased significantly with tumor size ($p = 0.0066$ for males and $p = 0.0224$ for females), and differences in rates of prolactin normalization after surgery with tumor size were only significant in males ($p = 0.0035$). Subgroup analysis of males presenting with hormone-related symptoms was performed (— **Table 5**) and showed that males who present with gynecomastia, galactorrhea, or decreased libido had smaller tumor sizes, though this was only statistically significant for galactorrhea ($p = 0.0030$). In addition, patients who present with galactorrhea appeared to have statistically significant lower prolactin levels at diagnosis and K_i-67 indices ($p = 0.0449$ and $p = 0.0158$, respectively). Patients with gynecomastia also appeared to have lower prolactin levels at diagnosis and lower K_i-67 indices, but this was not statistically significant.

Discussion

Gender differences in prolactinomas have been documented in previous studies; however, the reason for these differences has not yet been explained. Prolactinomas are more common in females, and this was confirmed in our series with more than twofold number of female patients compared with male patients in the time period of study.⁴ Moreover, in other series, females tend to be 10 years younger at the age of diagnosis, though this was not evident in our series with the age at the time of surgery being only slightly older in males.^{4,18} One thought is that the difference in incidence among the genders is related to differences in clinical presentation. As stated previously, the clinical manifestation of hyperprolactinemia in men and women differ in that men tend to have more insidious, and often clinically underestimated, symptoms of low libido and erectile dysfunction,

Table 2 Summary of medical treatment prior to surgical intervention

	Males (n = 22)	Females (n = 57)	p-Value
Medical treatment with DA			
Yes	20	52	0.9643
No	2	5	
Prolactin level response to medical therapy			
No	2	12	0.4813
Partial	11	24	
Complete	7	14	
Tumor size reduction			
No	10	32	0.3737
Yes	10	20	
Length of medical therapy (mo)	31.75	32.43	0.9499
Reasons for pursuing surgery (%)			
Side effects to DA	7 (31.8%)	26 (45.6%)	
Partial/no response to DA	9 (40.9%)	36 (63.2%)	
Persistent/worsening symptoms	8 (36.4%)	15 (26.3%)	
Patient preference	0 (0%)	2 (3.5%)	
Desire for pregnancy	N/A	8 (14.0%)	

Abbreviations: DA, dopamine agonist; N/A, not available.

Table 3 Operative outcomes

	Males (n = 22)	Females (n = 57)	p-Value
Resection			
Gross total	15	53	0.0086
Subtotal	7	4	
Normalization of PRL 2 mo after surgery			
Yes	13	52	0.0019
No	9	5	
Complications			
Yes	20	51	1.000
No	2	6	
Intraoperative CSF leak			
Yes	5	9	0.5177
No	17	48	
Length of stay (d)	2.90	2.32	0.2885
Postoperative radiation			
Yes	2	2	0.3087
No	20	55	
Required medical therapy postoperative			
Yes	7	7	0.0536
No	15	50	

Abbreviations: CSF, cerebrospinal fluid; PRL, prolactin.

compared with females who present most often with menstrual cycle irregularities; thus males would present at a later age.¹⁸ Our study confirmed this tendency, as the most common presenting symptom for males and females was decreased libido and menstrual irregularities, respectively. Support for the hypothesis that females present more often due to more obvious clinical signs and symptoms as opposed to a true increased incidence is found in autopsy studies where the prevalence of prolactinomas was similar in males and females postmortem.¹⁹ Another hypothesis points to hormonal differences between males and females leading to the difference in gender incidence, with one study showing greater incidence in females during child-bearing age, which becomes more even, in the fifth to seventh decades of life between the two genders.¹⁰ In addition, there have been case reports of prolactinomas induced in male-to-female transsexual patients, possibly due to hormonal therapy, though causation cannot be definitively determined in these cases.²⁰⁻²³

The analysis from this study also revealed that males had significantly larger tumors and thus more symptoms related to mass effect, such as visual disturbances, compared with females. In addition, men had significantly higher rates of cavernous sinus invasion and suprasellar extension, which are clinical markers of advanced and aggressive tumors. The difference in tumor size and presentation of males with visual disturbances has been well described in the literature.^{7,12,14,15,24} Most often, the differences in tumor size and aggressiveness are attributed to delays in detection in men; however, some findings have advocated for a difference in

Table 4 Subgroup analysis of male and female groups based on tumor size

Males				
	Micro (n = 7)	Macro (n = 12)	Giant (n = 3)	p-Value
Prolactin level at diagnosis (ng/mL)	172.0	960.4	12,404.3	
K _i -67 labeling index	2.14	2.92	18.33	
Subtotal resection (%)	0 (0%)	4 (33.3%)	3 (100%)	0.0066
Prolactin normalization after surgery (%)	7 (100%)	6 (50%)	0 (0%)	0.0035
Correlation	Spearman rho			p-Value
Tumor size to prolactin level at diagnosis	0.6184			0.0022
Tumor size to K _i -67 labeling index	0.4021			0.0636
Females				
	Micro (n = 34)	Macro (n = 23)	Giant (n = 0)	p-Value
Prolactin level at diagnosis	310.3	862.1	N/A	
K _i -67 labeling index	3.44	3.65	N/A	
Subtotal resection	0	4 (17.4%)	N/A	0.0224
Prolactin normalization after surgery	32 (94.1%)	20 (87.0%)	N/A	0.3837
Correlation	Spearman rho			p-Value
Tumor size to prolactin level at diagnosis	0.2267			0.0899
Tumor size to K _i -67 labeling index	0.1164			0.3886

Abbreviation: N/A, not available.

tumor biology to be the true cause of these differences. Studies have noted differences in tumor histopathological characteristics between the genders, with male tumors showing greater rates of cellular atypia and higher amounts of K_i-67 labeling index staining on histopathology.^{12,14,24,25} In our data, the male group did have more diagnoses of atypical adenoma and did show a slightly higher K_i-67 labeling index; however, these findings were not significant. Other studies have presented evidence that differential expression of estrogen receptor α and transforming growth

factor β 1 may play a role in the difference seen in tumor pathogenesis between the genders, though the results of these studies are yet to be confirmed.^{13,26}

Previous studies have also shown differences in disease history between men and women with prolactinomas. Specifically, men have been previously shown to have shorter duration of symptoms prior to surgery, higher levels of preoperative serum prolactin levels, and more medically refractory disease.^{12,14,15,24,27,28} Males in our patient population did have higher prolactin levels at diagnosis, but this

Table 5 Subgroup analysis of males with hormonal symptoms at presentation

	BMI (kg/m ²)	Tumor size (mm)	PRL level at diagnosis	Subtotal resection	K _i -67 labeling index
Gynecomastia					
No (n = 13)	31.75	21.69	3,312.9	6 (46.1%)	6.38
Yes (n = 9)	33.65	14.89	790.4	1 (11.1%)	2.44
p-Value	0.4811	0.1624	0.1599	0.1649	0.1241
Galactorrhea					
No (n = 20)	33.03	19.95	2,495.1	7 (35%)	5.15
Yes (n = 2)	27.44	8.50	140.0	0 (0%)	1.00
p-Value	0.3879	0.0030	0.0449	0.5454	0.0158
Decreased libido					
No (n = 11)	33.79	21.91	2,337.9	4 (36.4%)	5.36
Yes (n = 11)	31.26	15.91	2,224.1	3 (27.3%)	4.18
p-Value	0.3438	0.2399	0.9566	1	0.6940

Abbreviations: BMI, body mass index; PRL, prolactin.

was not statistically significant. There was no difference in length of medical therapy between the groups. Females in our study group did have a greater percentage of patients who had completely medically resistant tumors to dopamine-agonist therapy. When grouping together the nonresponsive and partially responsive tumors in each gender, the rates were very similar at 59% for males and 63% for females. This is in contrary to previous reports which have noted that dopamine-agonist-resistant prolactinomas tend to be larger in size, have increased angiogenesis, have more cellular atypia, have increased invasiveness, and are more likely in male patients.²⁸

There were also notable outcomes differences between the two genders noted in our study. Males were found to have significantly lower rates of gross total resection, normalization of prolactin levels 2 months after surgery, and were approaching significance for requiring continued medical therapy with a dopamine agonist following surgery. These findings are in line with previous reports which have shown lower rates of remission in men than in women.^{7,13,27} It is likely that the rate of remission after surgery is related to the size and invasiveness of the tumors, as this would make intuitive sense. However, a previous study showed that cavernous sinus invasion was associated with lack of remission postoperatively in univariate analysis but not in multivariate analysis.⁷ In addition, a review of surgical removal of microprolactinomas showed high remission rates of 83 to 100% when performed by experienced surgeons, lending credence to size being a factor in outcomes.¹

In our subgroup analyses, we found that the prolactin level at diagnosis is related to tumor size, an association which is already been described.⁹ There was a significant correlation between tumor size and K_i-67 labeling index in males but not in females. However, this is likely due to the fact that there were not any female patients with giant prolactinomas included in the study group, with the largest female tumor at 28 mm in size. As would be expected, our results showed that patients with microadenomas were significantly more likely to have gross total resections in both genders. Subgroup analysis of males with hormone-related symptoms (gynecomastia, galactorrhea, and decreased libido) revealed that these patients tend to present with smaller tumor sizes, lower levels of prolactin at diagnosis, and lower K_i-67 labeling indices, of which these were only statistically significant for patients presenting with galactorrhea. Of note, there was no statistically significant difference in body mass index between males with gynecomastia and males without gynecomastia, with averages of 33.68 and 31.75, respectively ($p = 0.4811$). These findings may represent that male patients presenting with hormone-related symptoms may have biologically different tumors which behave more like female prolactinomas than males who present with compressive symptoms. However, due to limited number of patients in this analysis, further study is warranted to draw any conclusions.

As noted previously, delays in detection of prolactinomas in males compared with females are the most commonly cited reason for differences in clinical presentation and outcomes between the two genders. There have also been

studies which point to tumor biology, through histopathological analyses and evidence of dopamine-agonist resistance, as the cause of these differences in presentation and outcomes. It is likely that the differences noted in the two genders are a combination of both theories. Current clinical practice guidelines set forth by the Endocrine Society recommend morning testosterone testing in males with signs and symptoms of hypogonadism, including low libido and erectile dysfunction and further testing of the pituitary axis only if this laboratory test should prove to be abnormal.²⁹ However, normal testosterone levels may be seen in patients with mild hyperprolactinemia and in up to 30% of patients with prolactinomas.³⁰ Due to this, clinicians should keep in mind the possibility of a prolactinoma in male patients who present with persistent symptoms of hypogonadism, even when previous testosterone testing has been within the normal range.

There are several limitations to our study. Our patient cohort were selected from patients who underwent surgery for their prolactinomas and not all patients with prolactinomas, which may explain some of the differences in results from previous studies, through the introduction of selection bias. As the patients at our tertiary referral institution were more often initially treated at outside centers, some of the data collected may have been subject to recall bias, including presenting symptoms, initial dopamine level at diagnosis, and length of medical therapy. In addition, four patients had previously undergone surgical treatment for their prolactinoma at other institutions; however, due to the low number, they were not included in the analysis.

Conclusion

In this retrospective series, we found that male prolactinoma patients undergoing surgical therapy differ significantly from female prolactinoma patients, with larger tumor sizes, higher frequency of suprasellar extension, and higher frequency of cavernous sinus invasion. Females were also significantly more likely to receive gross total resection during their operations and have normalization of their serum prolactin levels 2 months after surgery compared with males. We also confirmed previous findings that there are differences in presenting symptoms described between males and females, with males presenting more often with decreased libido, whereas females presented most often with menstrual irregularities and galactorrhea. Earlier diagnosis in males may improve outcomes, but this is a diagnostic challenge due to the subtle clinical presentation in males compared with females.

Note

A portion of the data presented in this article was presented at the North American Skull Base Society meeting on March 3–5, 2017, in New Orleans, LA.

Conflict of Interest

There is no financial disclosure or conflict of interest to disclose for any of the authors.

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