Neuroendocrinology Letters No.2 April Vol.26, 2005

ORIGINAL ARTICLE

Gender-related Differences in Prolactinomas. A clinicopathological study

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Submitted: September 4, 2004 *Accepted: February 1, 2005*

Key words: **gender; outcome; prolactinoma; pituitary adenoma**

Neuroendocrinol Lett 2005; **26**(2):152–159 **PMID:** 15855888 NEL260205A09 © Neuroendocrinology Letters **www.nel.edu**

Abstract

BACKGROUND/AIMS*:* Prolactinomas are the most common tumors of the pituitary gland. Only few studies have documented gender-related differences in the growth and presentation of these tumors, but nothing is known about their effects on their subsequent surgical outcome and prognosis.

PATIENTS & METHODS*:* Twenty-six patients with prolactinomas, that met strict immunohistochemical and electron microscopic criteria and were surgically treated between January 1990 and June 1997, were retrospectively reviewed. The patient charts, as well as histological (mitotic index) immunohistological (MIB-1 labeling-index) and electronic microscopical staining were analyzed.

RESULTS*:* Nineteen patients were women, and seven were men; the female-to-male-ratio was 2.7:1. Men were significantly older, both at diagnosis and surgery. Menstrual abnormalities were the most common presenting symptom in women, whereas impotence predominated in men. Psychological symptoms were significantly more common in men than in women. Men had a significantly shorter preoperative duration of symptoms and higher preoperative serum prolactin levels than women. The preoperative prolactin levels and proliferative activities (mitotic index, MIB-1 labeling index) were lower in women compared to men and showed a direct correlation to postoperative outcome. The overall outcome was significantly better in women than in men. In women, age less than 35 years was a beneficial prognostic factor, and preoperative bromocriptine treatment was associated with a significantly worse long-term-outcome.

CONCLUSION*:* The biology and the clinical course of prolactinomas seem to differ in women and men. In men, the preoperative durations of symptoms is shorter, the tumors are larger and more invasive at surgery, and the outcome is worse than in women. Based on proliferative activities (mitotic index, MIB-1 labeling index), the predominance of marcoadenomas in men is due to a high frequency of rapidly growing tumors, which are often invasive and frequently correlated with a worse outcome. Our findings may justify a more aggressive therapeutic approach to prolactinomas in men than in women.

Introduction

In both autopsy and surgical series, adenomas that secrete prolactin (PRL) are the most common pituitary tumors, accounting for 30% to 40% of all tumors in that anatomical location [1–4]. The few studies of gender-related differences in prolactinomas have documented a marked preponderance of these tumors in females [1,3–10], but also in other pituitary adenomas [11,12]. Macroprolactinomas are slightly more common in women than in men, and men rarely present with microadenomas [11–14], that represent the great majority of prolactinomas. The reason for the preponderance of large tumors in men remains to be elucidated. Hitherto, it remains unclear whether this finding reflects a delay in diagnosis or gender-specific differences in tumor pathogenesis [15–24].

Micro- and macroprolactinomas show substantial differences in their natural history [19] response to bromocriptine [25], anatomy [19,26,27] and effects on surrounding brain tissue structures [22,28]. The impact of these differences is not yet understood. There may also be gender-related differences in the biological behavior of these tumors in men compared to women: recent data suggest that a subset of men may have rapidly growing prolactinomas with increased markers of cellular proliferation [5]. It is unclear whether this findings reflect a delay in diagnosis or gender-specific difference in tumor pathogenesis. The few available data on the effect of gender on outcome in prolactinomas show a less favorable postoperative outcome in men than in women [4,5,29].

To determine the nature and extent of gender-related differences in prolactinomas, a series of surgically treated prolactinomas was retrospectively reviewed with special reference to gender-related differences in the surgical outcome and prognosis of macroprolactinomas, based on clinicopathological parameters.

Patients and Methods

Patient Population. The charts of patients, who underwent surgical treatment for pituitary adenoma between January 1990 and June 1997 at the University Hospitals of Basel, Switzerland, were retrospectively reviewed. Patients who had multiple pituitary procedures were included only if the first operation was performed at the University Hospitals of Basel; these patients were counted only once. Prolactinoma was diagnosed solely on the basis of immunohistochemical and/or electron microscopic findings. Prolactinomas were defined as pituitary adenomas that immunostained positively for PRL or that met the hormonal, ultrastructural morphologic, and cytogenetic criteria established by Asa [7]. Pluri- and pleurihormonal adenomas were not counted as prolactinomas even if one of the hormones secreted was PRL. Adenomas with the clinical phenotype of prolactinoma were not included in the study if immunohistochemical or electron microscopic analysis did not reveal a PRL-producing adenoma (*e.g.,* an endocrine-inactive pituitary adenoma causing increased serum-PRL through the stalk effect).

All patients underwent preoperative endocrine testing and neuroradiological examinations, including cerebral computed tomography (CT), cerebral magnetic resonance (MR) imaging, digital subtraction arteriography of cerebral blood vessels, or MR arteriography of cerebral blood vessels. Pituitary function was assessed by means of basal and dynamic testing. Measurement of serum free thyroid-stimulating hormone (TSH), prolactine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone in men and estradiol in premenopausal women, cortisol, and urinary free cortisol level permits to identify patients requiring specific replacement therapies. Plasma PRL concentrations were measured by radioimmunoassay before surgery, 10 to 14 days postoperatively, and every 6 to 12 months thereafter. At our institution, the normal serum-PRL is 1.9 to 16.0 ng/ml for men and 2.0 to 17.0 ng/ml for women. Preoperatively, none of the patients had been treated with radiation therapy. Tumors were graded according to Hardy's classification [30] as modified by Wilson [14]. For all operations, a standard transsphenoidal approach and a surgical microscope were used.

The outcome was divided into three categories:

(i) *remission*: serum-PRL levels and clinical signs and symptoms normalized within 12 weeks after surgery and remained stable during follow-up; (ii) *recurrence:* serum-PRL levels and clinical signs and symptoms normalized within 12 weeks after surgery, but a clinical relapse occurred during follow-up; (iii) *persisting disease:* clinical signs and symptoms did not normalized within 12 weeks after surgery.

Histological Examination. All specimens were fixed in formalin, embedded in paraffin, and stained by the haemtoxlin-eosin method. The histological diagnosis of pituitary adenoma was confirmed, and the mitotic index was assessed semiquantitatively and expressed as 0, 1 or more than 1 mitoses per 10 high-power (x400) fields.

Immunohistochemistry. Measurements of cell proliferation were based on MIB-1 (monoclonal antibody, Dianova Hamburg, Germany, lot 006, dilution 1:1000) labeling indices. Sections were systematically examined on high-power fields (x400) for the presence of immunoreactivity. The areas with the highest density of MIB-1 labelling index (LI) was assessed by counting at least 1000 adjacent cells in the selected areas.

Statistical Analysis. Data are reported as the mean ± standard deviation (SD) unless otherwise indicated. The nonparametric Wilxcoxon two-sample rank-sum test was used to compare the geometric means of the study groups.). Relationships between tumor size and PRL basal levels were tested using linear regressions. The frequency of observations between men and women was compared by the unpaired t-test and the Fisher's exact test where appropriate. The level of significance was set at $p < 0.05$.

Results

Twenty-six patients met the inclusion criteria. Nineteen (70%) were women, and seven (30%) were men; the female-to-male ratio was 2.7:1 (Table 1). Men were significantly older, both at diagnosis (46 ± 22 (range 18–71) versus 28 ± 12 (range 16–65) years; $p < 0.05$) and at surgery (48 ± 18 (range 23–72) versus 30 ± 14 (range 16–65) years; $p < 0.04$). In men, prolactinomas occurred with about the same frequency in all age groups, whereas there was a marked peak occurrence in women before the age of 45. Eight (31%) of the tumors were microadenomas, and 18 (69%) were macroadenomas. The mean tumor size was 15 ± 9 mm overall (8 ± 2 mm for microadenomas and 16 ± 5 mm for macroadenomas). Age at diagnosis did not correlate with tumor size in men or women.

Clinical Features. Menstrual abnormalities were the presenting symptom in 84% of the female patients (Table 1). Of the 15 women with amenorrhea, six (40%) had a microprolactinoma, and nine (60%) had a macroprolactinoma. The one patient with oligomenorrhea had a macroprolactinoma. Tumor size did not correlate with menstrual abnormalities. Women presenting with amenorrhea had a longer preoperative duration of symptoms (58 ± 28 versus 30 ± 19 months; $p < 0.007$) and a higher preoperative serum-PRL level (807 ± 1343 versus 188 ± 202 ng/ml; p: NS) than those with other presenting endocrine symptoms. Four of seven men (57%) had impotence, which was the most common symptom in men. Men had a significantly shorter preoperative duration of symptoms (24 ± 12 versus 46 ± 22 months; $p < 0.007$) and higher preoperative serum-PRL levels (3632 ± 3839 versus 677 ± 49 ng/ml; p: NS) than women. The duration of symptoms before diagnosis was not predictive of tumor size. Significantly more men than women had psychological symptoms, as depression, psychotic symptoms, irritability (57% versus 5%; $p < 0.03$). Men with MIB-1 LI above than the mean of the whole collective (1.2+/–2) tended to be older than those who were below, but the difference was not statistically significant.

Tumor Characteristics. Men had larger tumors (22 ± 11 versus 14 ± 8 mm; p: NS) and presented more frequently with invasive tumors (57% versus 26%; $p < 0.03$) than women (Table 2). Microprolactinomas were exclusively seen in women, and macroprolactinomas were more common in men than women (100% versus 58%; p: NS).

A positive correlation between basal PRL level and the tumor size was observed ($R=0.735$; $p> 0.001$; Table 1). Although the correlation ratio was significantly high in women ($R=0.876$), it was low in men (($R=0.382$).

Mitotic indices expressed as 0,1, or more than 1 per 10 hpf is listed in Table 3. Presence or absence, as well as the total number of mitoses per 10 hpf was not associated with tumor size or invasiveness. However, the mitotic activity was significantly related to prolactin levels ($p < 0.03$). MIB-1 labeling indices were higher in adenomas of male patients (Table 3). Mitotic activity was associated with higher MIB-1 levels ($p < 0.04$). The data suggested no relationship between proliferative activity (MIB-1 labeling index), tumor size or invasion.

Surgical Characteristics. The indications for surgery differed in men and women. The most common indications were rapid progression of mass effect in men (86%), whereas in women it was only 16% (Table 4). Preoperatively, 14 of 19 women (74%), including all seven with microprolactinomas and seven of 11 (64%) with macroprolactinomas, were treated with bromocriptine (N=6; 86%). Four of seven men (57%), all with macroprolactinomas, also received preoperative medical treatment.

Outcome. The mean duration of follow-up was 19 ± 11 months and was not significantly different in men and women (18 ± 7 versus 20 ± 12 months, respectively). The overall outcome was significantly better in women than in men (Table 5): remission in 89% versus 43% ($p < 0.03$). One of 10 women (10%) and two of three men (66%) showed symptomatic tumor recurrence 4 to 8 months after operation with initial remission. In cases of remission, age less than 35 years was a beneficial factor in women, whereas in men it seems that an age over 35 may be associated with a better outcome (Table 6). With regard to preoperative serum prolactin levels, we noted statistical relationship to gender ($p < 0.04$), tumor size ($p < 0.05$), the presence or absence of invasion ($p < 0.04$) and pro-

TABLE 1: *Clinical features according to gender*

Clinical Feature	Female (n = 19)	Male (n = 7)	Total (n = 26)
Mean age (yr) at onset (± SD)	28 ± 13	48 ± 18	34 ± 17
Mean duration of symptoms (month) at onset (±SD)	46±22	24±12	29±15
Focal neurological deficit			
Visual field deficit	4 (21%)	3 (43%)	7 (27%)
Visual impairment	1 (5%)	3 (43%)	4 (15%)
Psychological deterioration	1 (5%)	4 (57%)	5 (19%)
Endocrine manifestations			
Primary amenorrhea	1 (5%)	NA	1 (4%)
Secondary amenorrhea	14 (74%)	NA	14 (54%)
Oligomenorrhea	1 (5%)	NA	1 (4%)
Galactorrhea	9 (47%)	NA	9 (35%)
Hirsutism	3 (16%)	NA	3 (12%)
Hypogonadism	4 (21%)	5 (71%)	9 (35%)
Gynecomastia	NA	2 (29%)	2 (8%)
Delayed puberty	1 (5%)	NA	1 (4%)
Impotence	NA	4 (57%)	4 (15%)
Preoperative serum PRL level (±SD)	677±1229	3632±4076	2893±3356
Partial hypopituitarism	6 (32%)	5 (71%)	11 (42%)
Panhypopituitarism	1 (5%)	1 (14%)	2 (7%)
PRL-level/tumor size (mean)	48	165	193

SD = standard deviation; NA = not applicable; PRL = prolactin.

TABLE 2: *Anatomical classification and other tumor characteristics according to gender*

Tumor Characteristics	Female (n = 19)	Male (n = 7)	Total (n = 26)
Grade I (<10 mm)	8 (42%)	NA	8 (31%)
Stage 0	8 (42%)	NA	
Grade II (>10 mm)	6 (32%)	3 (43%)	9 (35%)
Stage 0	4 (21%)	2 (29%)	
Stage A	1 (5%)	NA	
Stage B	1 (5%)	1 (14%)	
Grade III (locally invasive)	3 (16%)	2 (29%)	5 (19%)
Stage C	2 (11%)	NA	
Stage D	1 (5%)	2 (29%)	
Grade IV (diffusely invasive)	2 (11%)	2 (29%)	4 (15%)
Stage C	1 (5%)	NA	
Stage D	NA	1 (14%)	
Stage E	1 (5%)	1 (14%)	
Median tumor size (mm ± SD)	14 ± 8	22 ± 11	15 ± 9
Cystic tumor	2 (11%)	1 (14%)	3 (12%)

SD = standard deviation; NA = not applicable.

TABLE 3: *Cell proliferation data according to gender in 26 patients with prolactinomas*

Factor	Female (n = 19)	Male (n = 7)	Total (n = 26)
Microadenoma	8 (42%)	NA	8 (30%)
Mitoses/10 hpf			
– 0	100%	0%	30%
– 1	0%	0%	0%
– >1	0%	0%	0%
MIB-1 LI;			
– mean ± SD	0.6±2	1.3±3	0.9±2
– range	0–7.2	0.0–5.2	0–7.6
Microadenoma	6 (32%)	3 (43%)	9 (35%)
Mitoses/10 hpf			
– 0	82%	29%	27%
– 1	18%	14%	8%
– >1	0%	0%	0%
MIB-1 LI;			
– mean ± SD	0.9±2	1.9±3	1.2±2
– range	0–7.7	0.1–7.2	0–9.6
Invasive Adenoma	5 (26%)	4 (57%)	9 (35%)
Mitoses/10 hpf			
– 0	84%	57%	76%
– 1	16%	29%	19%
– >1	0%	14%	4%
MIB-1 LI;			
– mean ± SD	1.0±2	1.9±3	1.2±2
– range	0–9.6	0.2–9.2	0–9.6

hpf = high-power (x400) fields; LI = labeling index;
SD = standard deviation.

TABLE 4: *Indications for operation according to gender in 26 patients with prolactinomas*

Indication for operation	Female (n = 19)	Male (n = 7)	Total (n = 26)
Mass effect	3 (16%)	6 (86%)	9 (35%)
Apoplexy	1 (5%)	NA	1 (4%)
Bromocriptine resistance [1)]	9 (47%)	1 (14%)	10 (38%)
Desire for pregnancy	6 (32%)	NA	6 (23%)

NA = not applicable.
1) definition: prolactinomas that do not positively respond to medical treatment by bromocriptine.

TABLE 5: Gender-related differences in long-term outcome in patients with micro- and macroprolactinomas

	Female/Male Distribution [n (%)]		
	Micro-prolactinoma	Macro-prolactinoma	Total
Characteristic	(n = 8/0)	(n = 11/7)	(n = 19/7)
Remission	7 (88)/NA	9 (82)/2 (29)	15 (79)/2 (29)
Recurrence	NA/NA	1 (9)/2 (29)	1 (5)/2 (29)
Persisting disease	1 (12)/NA	1 (9)/3 (43)	3 (16)/3 (43)

NA = not applicable

liferative activity (mitotic activity and MIB-1 labeling indices; $p < 0.02$) compared to outcome (Table 7). No medical treatment up to a few days before operation was a beneficial factor for remission after surgery (8 of 8 patients (100%) vs. 12 of 18 patients (67%); Table 8). All persisting disease occurred in patients with preoperative medical treatment. The data suggested no relationship between proliferative activity (MIB-1 labeling index, mitotic activity) and preoperative medical treatment or not.

Discussion

This study of surgically treated and histologically proven prolactinomas, demonstrates gender-related differences in tumor biology and outcome. The effect of gender on outcome of prolactinomas has not been widely discussed in the literature, and we are the first to address this issue in a series of patients whose tumors met strict immunohistochemical and electron microscopic criteria. Until now, the discrepancy in gender distribution and outcome has been analyzed only in terms of the peak occurrence, growth and outcome of these tumors in various age groups.3–5 Here can be shown that there are gender-related differences not only in overall surgical outcome but also in the duration of symptoms, in presenting signs and symptoms, in tumor size, and in restoration of normal serum-PRL levels. The present results give substantial evidence that prolactinomas are different entities in women and men.

Clinical Manifestations. In almost all premenopausal women with prolactinomas, the initial symptoms are menstrual irregularities, galactorrhea, or infertility. In a summary of 17 series that included 1073 women with prolactinomas undergoing transsphenoidal surgery,

TABLE 6: *Gender-related differences in cases of total remission according to age and tumor size*

Age (yr)	Micro-prolactinoma (n=8)	Macro-prolactinoma (n=18)
Women	(n=8)	(n=11)
(1) < 35	6 (75%)	8 (73%)
- Mitoses/10 hpf		
0	0%	0%
1	0%	0%
>1	0%	0%
- MIB-1 LI		
mean±SD	0.5±1	0.2±0.3
range	0-1.6	0-0.8
(2) > 35	1 (13%)	2 (18%)
- Mitoses/10 hpf		
0	0%	0%
1	100%	0%
>1	0%	0%
- MIB-1 LI		
mean±SD	0.4	1.1±1
range	0.1-0.5	0.2-2
Men	(n=0)	(n=7)
(1) < 35	NA	NA
(2) > 35	NA	3 (42%)
- Mitoses/10 hpf		
0	NA	100%
1	NA	0%
>1	NA	0%
- MIB-1 LI		
mean±SD	NA	0.5±0.2
range	NA	0.2-0.6

NA = not applicable; hpf = high-power (x400) fields; LI = labeling index; SD = standard deviation.

TABLE 8: *Gender-related outcome 3 months after operation according to preoperative medical treatment*

	Female/Male Distribution [n (%)]		
	Micro-prolactinoma	Macro-prolactinoma	Total
Preoperative Treatment	(n = 8/0)	(n = 11/7)	(n = 19/7)
Medical treatment (>3 mo)			
Remission	6 (75)/NA	6 (55)/NA	12 (63)/NA
– Mitoses/10 hpf			
0	0%/NA	0%/NA	0%/NA
1	0%/NA	0%/NA	0%/NA
>1	0%/NA	0%/NA	0%/NA
– MIB-1 LI			
mean±SD	0.5±1/NA	0.43±/NA	0.47±1/NA
range	0–1.6/NA	0–2/NA	0–2/NA
Persisting disease	1 (12)/NA	1 (9)/4 (57)	2 (11)/4 (57)
– Mitoses/10 hpf			
0	0%/NA	0%/25%	0%/25%
1	100%/NA	100%/50%	100%/50%
>1	0%/NA	0%/25%	0%/25%
– MIB-1 LI			
mean±SD	9.6/NA	1.8/2.9±4	5.7±6 /9±4
range	(4.0–10.5)/NA	NA/(0.4–9.2)	(1.8–9.6)|(0.4–9.2)
No medical treatment			
Remission	1 (13)/NA	4 (36)/3 (43)	5 (26)/3 (43)
– Mitoses/10 hpf			
0	0%/NA	0%/100%	0%/100%,
1	100%/NA	0%/0%	20%/0%
>1	0%/NA	0%/0%	0%/0%
– MIB-1 LI			
mean±SD	0.4±0.5/NA	0.3±0.3/0.5±0.2	0.3±0.2/0.5±0.2
(range)	(0–0.4)/NA	(0–0.6)/(0.2–06.)	(0–0.6)/(0.2–0.6)
Persisting disease	NA/NA	NA/NA	NA/NA

NA = not applicable; hpf = high-power (x400) fields; LI = labeling index; SD = standard deviation.

TABLE 7: *Gender-related differences in outcome according to preoperative serum prolactin values and tumor characteristics (N (%))*

	Female		Male		Overall	
Characteristics	Remission (n=17)	Persisting disease (n=2)	Remission (n=3)	Persisting disease (n=4)	Remission (n=20)	Persisting disease (n=6)
s-PRL <200 ng/ml	8 (47)	1 (50)	3 (100)	NA	11 (55)	2 (33)
s-PRL >200 ng/ml	9 (53)	1 (50)	NA	4 (100)	9 (45)	4 (66)
Mitoses /10 hpf						
0	0%	0%	100%	25%	95%	17%
1	6%	100%	0%	50%	0%	66%
>1	0%	0%	0%	25%	0%	17%
MIB-1 LI						
mean±SD	0.4±1	5.7±6	0.5+0.2	2.9±4	0.4±1	3.8±4
range	0-1.6	1.8-9.6	0.2-0.6	0.4-9.2	0-1.6	0.2-9.6

s-PRL = serum prolactin; NA = not applicable; hpf = high-power (x400) fields; LI = labeling index; SD = standard deviation.

93% of patients had oligomenorrhea or amenorrhea and 83% had galactorrhea [22]. The lower incidence of galactorrhea in our patients (47%) may reflect the stringent histological criteria for entry into the present study. Nevertheless, galactorrhea was a much less common presenting symptom than expected. Presentation with focal neurological deficits due to large tumors is uncommon in women because they usually seek medical attention for menstrual dysfunction or galactorrhea, both of which generally occur even with minimal serum-PRL elevations and long before the tumors have grown large [31]. In contrast, men with prolactinomas seek treatment for symptoms relating to the size of the tumor rather than to impotence, loss of libido, or infertility. This difference probably reflects the lack of objective clinical markers to identify the onset of disease in men [5]. In a summary of 13 series that included 301 men with prolactinomas, not all of whom underwent surgery, 75% of patients were impotent, 38% had visual field defects, 35% had partial or complete hypopituita-

rism, and 12% had galactorrhea [22]. These findings are in accordance with ours. Thus, over one-third of men with prolactinomas have symptoms due to tumor size.

An interesting and little known feature of prolactinomas is their relationship to psychological deterioration. PRL modulates maternal functions and is involved in behavior [32]. PRL-binding sites have been identified in the hypothalamus and substantia nigra. Hyperprolactinemia stimulates dopamine turnover in several areas of the brain, including the nucleus accumbens, and reduces turnover in other regions (*e.g.,* the substantia nigra) [28,31]. It also stimulates the opioidergic system [31]. These biochemical features together with clinical observations suggest that hyperprolactinemia may play a role in the genesis or maintenance of mood abnormalities. Several authors have found a depressed mood, loss of interest in usual pleasures, irritability, and depressive and schizoid traits in women with prolactinomas and hyperprolactinemia [31,32]. However, psychological deterioration in men with prolactinomas has not been studied previously. Our results show that among patients with these tumors, men were significantly more likely than women to have psychological symptoms (43% versus 5%). Thus, mood abnormalities appear to be more common than previously suspected.

Tumor characteristics. Because prolactinomas are more common in women than in men [3], one might expect macroprolactinomas to be more common in women as well. Yet, even though the female to male ratio was 2.5:1 in the present series, macroadenomas were more prevalent in men (100% versus 58%). As a matter of fact, none of the men had a microprolactinoma. At the same time, the duration of symptoms was significantly shorter in men. These findings support the hypothesis that prolactinomas are different entities in women and men. One explanation for these gender-related differences would be faster tumor growth in men [5]. According to our results, the growth potential of macroprolactinomas seems greater in men than in women, given the preponderance of aggressive forms of the disease in men despite the higher prevalence of prolactinomas in women. The rarity of prolactinomas in women after the age of 45 years may also reflect less aggressive behavior of these tumors in females; the endocrine signs of prolactinomas disappear after menopause, and the tumor, if present, stays silent in women, whereas men develop symptoms of a pituitary mass [5]. In women, fewer than 7% of untreated microprolactinomas appear to increase in size over 4 to 6 years [33]. According to our numbers, this cannot be the case in men. However, the natural history of microprolactinomas in men is unknown, probably because of their rarity [5,34]. For this reason, our observations and those of other authors [5,32] suggest a fundamental, gender-related biological difference in the growth of prolactinomas. The difference is unlikely to be due to the differences in target organ sex hormones, since estrogens tend to be strongly growth promoting [35,36] explaining the higher frequency of prolactin in women. Because hyperprolactinemia causes gonadal suppression in both sexes, it is unlikely that gonad-inhibitory peptides such as inhibin or folliculostatin are important in the gender related difference of growth pattern [22]. It is not known whether other tumor growth factors exert gender-related differential effects on the growth of prolactinomas [37,38]. Another possibility is that the male and female reproductive axes have different sensitivities to hyperprolactinemia [22]. This may be underlined by the findings of the present study that correlation between PRL levels and tumor size was more significant in women than in men. In our series, amenorrhea and galactorrhea in women were associated with marginally elevated serum-PRL levels. In contrast, impotence and decreased libido in men were associated with much higher serum-PRL levels. These findings suggest that the male reproductive axis may be much more resistant to hyperprolactinemia. However, Spark, *et al.* [39], reported a number of men with mild hyperprolactinemia (serum-PRL levels of 19 to 90 ng/ml) unrelated to prolactinomas whose impotence was cured by lowering serum-PRL levels into the normal range with bromocriptine.

Outcome. In a summary of 32 series that included 2480 patients with prolactinomas, Molitch [22] found that 872 (72%) of 1224 microadenomas and 400 (32%) of 1256 macroadenomas were reported as being curatively resected, as demonstrated by the normalization of serum-PRL levels 1 to 12 weeks after surgery. The criterion for cure, however, is not uniform in these series, but a return of PRL levels to normal leads to a normal gonadal function in almost 100% of both sexes [22] The significant gender-related differences in surgical outcome and recurrence of our series are difficult to interpret. Comparable to Delgrange et al [5], basal PRL levels, mean tumor size and invasive tumors were significantly greater in men than in women and therefore may explain that men faired less favorably. Lastly, macroprolactionomas in males exhibited higher indexes of proliferating cells by Ki-67 immunoreactivity than do similar tumors in female patients [5]. For this reason, the higher incidence of recurrence in men may be due to a high frequency of rapidly growing and invasive tumors. Late recurrence of hyperprolactinemia would not be detected during a short follow-up period. In fact, in 58 women with microprolactinomas, Massoud, *et al* [40], noted late relapse of hyperprolactinemia in 43% within 10 to 20 years after operation. However, in most cases, the hyperprolactinemia was transient, lasting a few years and then disappearing with no other evidence of tumor recurrence. Disturbances of the normal release of inhibiting factors through postoperative "scarring" of the portal system may cause a partial stalk effect, resulting in slightly elevated PRL levels.

Since patients with larger tumors and higher serum-PRL levels were more likely to receive preoperative treatment with the dopamine agonist bromocriptine, it is not surprising that patients who received bromocriptine before surgery had a less favorable long-term-outcome. In general, macroadenomas are strikingly more sensitive than microadenomas to bromocriptine, perhaps because these larger tumors

are more sensitive to inhibition of PRL secretion [25] Nevertheless, a few patients with macroprolactinomas have been described in whom bromocriptine failed to maintain reduction in tumor size unless serum-PRL levels were reduced [18,41]. However, most series suggest that bromocriptine has little or no effect on later surgical results for microadenomas [27]. For macroadenomas, pretreatment with bromocriptine for more than 6 to 12 weeks jeopardizes the surgical outcome [17,28,42,43], most probably by causing perivascular fibrosis [27], hyalinosis of blood vessels, and tumor cell necrosis [44], which may render total resection more difficult or even impossible [42]. For this reason, restoration of normal serum-PRL levels after surgery seems to be less frequent in patients treated preoperatively with dopamine agonists [25,45].

Although our findings coincide with these reports, bromocriptine-induced changes in tumor morphology over time [26,29,42,45] would not explain the gender-related differences in outcome according to preoperative serum-PRL levels or the proliferative activities of the tumor in the present series. Our results support the hypothesis that microadenomas and macroadenomas are distinct entities [22]. In addition to the differences in their natural history [22–24], these tumors have different anatomical features. Capillaries are less frequent in macroadenomas than in the normal anterior lobe or in microadenomas [26], which implies a different tumor morphology that may explain the different response to medical treatment. In several series, preoperative serum-PRL levels >200 ng/ml were thought to decrease the chance for a surgical cure, even when patients were stratified by tumor size [4,17,44]. Our data suggest that the level of serum-PRL correlates with the proliferative activity of the tumor both in women and men. Other authors indicated that prolactinomas in male and older female patients have higher MIB-1 labeling indices than those of young female patients and conclude that in female patients the endocrine milieu or reproductive status may affect the proliferative activity of their prolactinomas [46,47]. In our opinion, it seems more reasonable that prolactinomas show not only gender-related differences in clinical presentation but also in surgical outcome, most likely because these tumors have greater proliferative potential in men [5]. Our findings justify a more aggressive therapeutic approach to prolactinomas in men than in women.

Conclusions. The tumor biology and the clinical course of prolactinomas appear to differ in women and men. In men, the preoperative duration of symptoms is shorter, the tumors are larger and more invasive, and the clinical outcome as well as the recurrence rate is worse than in women. Based on proliferative activities (mitotic index, MIB-1 labeling index), the predominance of Marco adenomas in men is due to a high frequency of rapidly growing tumors, which are often invasive and frequently correlate with a worse outcome. Our findings may justify a more aggressive therapeutic approach to prolactinomas in men than in women.

Acknowledgment. The author thanks Markus Tolnay, M.D., Neuropathology, University Hospitals, Basel, Switzerland, for histologic examinations and immunohistochemestry of the surgical specimens as well as his helpful discussion.

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