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Primary Medical Therapy of Micro- and Macroprolactinomas in Men*

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ABSTRACT

The presentation and long-term therapeutic responses of PRL-secreting pituitary tumors in men have been only partially studied. Gender-specific differences in tumor size at clinical presentation and possible differences in tumor biology in men compared to women make it important to determine treatment outcomes of male patients with prolactinomas.

We performed a retrospective review of men with prolactinomas medically managed at Massachusetts General Hospital between 1980 and 1997. We identified 46 male patients with prolactinomas managed with medical therapy alone. Twelve patients had microadenomas, defined as a serum PRL level greater than 15 ng/mL and a normal pituitary scan or a tumor smaller than 1 cm. Thirty-four patients had macroprolactinomas, defined by a serum PRL greater than 200 ng/mL and pituitary adenoma larger than 1 cm. Bromocriptine, quinagolide, and/or cabergoline were administered as medical therapy. All patients had at least one follow-up visit, and the most recent serum PRL measurement after initiating dopamine agonist therapy was reported.

Baseline clinical characteristics for patients with macroprolactinomas and microprolactinomas showed a larger proportion of patients with macroprolactinomas reporting a history of headache (74% *vs.* 0%), whereas the prevalence of sexual dysfunction and testosterone deficiency was similar between the two groups. Median serum PRL at presentation was 99 ng/mL (range, 16–385 ng/mL) *vs.* 1415 ng/mL (range, 387–67,900 ng/mL), in the microprolactinoma and macroprolactinoma groups, respectively.

A normal PRL level was achieved in a similar percentage of men with microprolactinomas *vs.* macroprolactinomas (83% *vs.* 79%, respectively). Although the majority of patients in both groups were treated with bromocriptine, a comparable number of patients with microprolactinomas *vs.* macroprolactinomas achieved a normal PRL level with cabergoline therapy. The response rates for bromocriptine and cabergoline were similar in both groups. No patient with a microprolactinoma required hormone replacement therapy, in contrast to patients with macroprolactinomas, who required thyroid, testosterone, and/or glucocorticoid replacement therapy. No patient had evidence of an increase in tumor size during therapy.

In summary, we investigated the clinical presentation and treatment outcome in men with prolactinomas. We found that normalization of serum PRL levels occurs in approximately 80% of men with prolactinomas. Of importance, dopamine agonist administration yielded similar biochemical remission rates in men with microprolactinomas and macroprolactinomas. (*J Clin Endocrinol Metab* **85:** 3053–3057, 2000)

THE CLINICAL manifestations and response to therapy of prolactinomas in women are well described. However, there are scant clinical data available regarding PRL-secreting pituitary tumors in men. In women, even minor elevations in serum PRL levels often lead to symptoms of ovulatory dysfunction and/or galactorrhea, leading to early diagnosis. In men, PRL elevations typically lead to hypogonadism, with decreased libido, erectile dysfunction, and abnormal semen analysis (1–3). Because of the insidious nature of these symptoms and signs in men and the lack of a defined objective history, diagnosis is often delayed. There are gender-specific differences in tumor size at clinical presentation, such that microprolactinomas are more commonly found in women compared to macroadenomas in men (4). It is unclear whether this finding reflects a delay in diagnosis or gender-specific differences in tumor pathogenesis. There may also be differences in the biological behavior of 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 (4, 5). Despite these findings, few studies have addressed the clinical and biochemical presentation as well as the response to dopamine agonist administration for prolactinomas specifically in men. We therefore performed a retrospective chart review to compare the presentation, medical management, and treatment outcomes of male patients with microprolactinomas and macroprolactinomas.

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Subjects and Methods

Patients

Patients were identified by screening case records from the Neuroendocrine Clinical Center at the Massachusetts General Hospital. Inpatient records at Massachusetts General Hospital between 1980 and 1997 were identified by searching the hospital medical record database using the ICD-9 code for benign pituitary neoplasm. Patients with either acromegaly or Cushing's disease were excluded. From approximately 1000 charts, we identified 123 males with prolactinomas, including 46 case records of men with prolactinomas evaluated and treated solely with medical management. Inclusion criteria for microadenomas were 1) an elevated serum PRL (>15 ng/mL) and a normal computed tomography (CT) or magnetic resonance imaging (MRI) scan of the pituitary, with no other explanation for increased PRL, such as primary hypothyroidism or drug-induced hyperprolactinemia; or 2) an elevated serum PRL and a tumor less than 1 cm in diameter. Inclusion criteria for

macroprolactinomas included a serum PRL level greater than 200 ng/mL, and a pituitary tumor more than 1 cm in diameter on pituitary CT or MRI scan. Based on these criteria, of the 46 cases, 34 patients had macroprolactinomas and 12 had microprolactinomas.

Clinical history, including presenting chief complaint, physical examination, serum PRL and testosterone levels, pituitary hormone assessment, tumor size by pituitary CT or MRI scan, and visual field testing, was recorded. Testosterone levels were analyzed in reference to patient age-adjusted normal ranges throughout the study. Medical therapies included bromocriptine, quinagolide, cabergoline, or pergolide. Sequential treatment with more than one dopamine agonist (DA) may have occurred due to drug intolerance, drug resistance, availability of quinagolide or cabergoline, or a combination of these factors. All patients had at least one follow-up visit and serum PRL measurement after initiating DA therapy. For any given clinical end point, follow-up data are reported if that parameter was evaluated on at least one occasion after initiation of DA therapy. If more than one follow-up measurement was taken for a specific clinical end point in an individual patient, the most recent value was reported. This study was approved by the subcommittee on human studies of Massachusetts General Hospital.

Serum total testosterone was determined by RIA (Diagnostics Products, Los Angeles, CA). Serum PRL levels were determined by previously described methods (6).

Statistical methods

For quantitative comparisons between males with microprolactinomas and macroprolactinomas, Wilcoxon's rank sum test, which is invariant to the distribution of the outcome variable, was used. For comparing prevalence and percentages in the two groups, Fisher's exact test was performed, with $P < 0.05$ considered significant.

Results

Assessment at presentation

Baseline clinical characteristics for patients with microprolactinomas *vs.* macroprolactinomas are shown in Table 1. Age was similar between the groups. Sexual dysfunction was equally prevalent between the two groups. Extrasellar extension was more prevalent in men with macroprolactinomas ($P < 0.01$). A larger proportion of patients with macroprolactinomas reported a history of headache (74% *vs.* 0%; $P < 0.01$) and visual abnormalities (37% *vs.* 0%; $P = 0.02$) than men with microadenomas.

The median serum PRL at presentation was significantly lower in patients with microprolactinomas and did not overlap with levels in subjects with macroprolactinomas (see Table 1). Serum testosterone levels were significantly higher in the microprolactinoma group ($P < 0.01$). Testosterone deficiency (<300 ng/dL) was present in 74% of patients with microprolactinomas compared with 93% of those with macroadenomas (P = NS).

Initial presenting complaints were assessed. The most frequent chief complaint for patients with macroprolactinomas was headache, which was described in 14 patients. No patient with microprolactinoma described headache as a chief complaint. Similar numbers of subjects with macroprolactinomas (n = 8) and microprolactinomas (n = 6) reported diminished libido as the chief presenting complaint. Other presenting complaints (n = 1 for each) included infertility, gynecomastia, visual disturbances, cerebrospinal fluid rhinorrhea, stroke, and breast sensitivity.

Follow-up evaluation

Mean duration of follow-up was comparable in both groups, as shown in Table 2. Eighty-three percent (95% confidence interval, 51.6, 97.9%) of men with microprolactinomas achieved

TABLE 1. Clinical and biochemical characteristics at presentation in patients with microprolactinomas and macroprolactinomas

Clinical and biochemical characteristics	Microprolactinomas (n = 12)	Macroprolactinomas (n = 34)
Age at diagnosis [yr; median (range)]	49 (16–72)	46 (19–74)
Diminished libido [no. (%)]	7/9 (78)	21/27 (78)
Impotence [no. (%)]	9/9 (100)	20/25 (80)
Headache [no. (%)][a]	0/6 (0)	14/19 (74)
Visual field abnormalities [no. (%)][a]	0/11 (0)	11/30 (37)
Extrasellar extension [no. (%)][b]	2/12 (17)	31/34 (91)
Testosterone [ng/dL; median (range)][b]	230 (103–538)	149 (18–476)
Testosterone deficiency [<300 ng/dL; no. (%)]	8/11 (74)	25/27 (93)
PRL [ng/mL; median (range)][b]	99 (16–385)	1415 (387–67,900)

[a] $P < 0.02$.
[b] $P < 0.01$.

TABLE 2. Clinical and biochemical characteristics during follow-up in patients with microprolactinomas and macroprolactinomas

Clinical and biochemical characteristics	Microprolactinomas (n = 12)	Macroprolactinomas (n = 34)
Follow-up [yr; median (range)]	4.0 (0.5–7.7)	4.4 (0.1–11.5)
Diminished libido [no. (%)]	4/9 (44)	11/27 (41)
Impotence [no. (%)]	6/10 (60)	11/23 (48)
Headache [no. (%)][a]	0/8 (0)	4/18 (22)
Visual field abnormalities [no. (%)]	0/2 (0)	3/16 (19)
Reduction in tumor mass [no. (%)]	1/6 (17)	9/27 (33)
Nadir testosterone [ng/dL; median (range)]	342 (170–579)	314 (10–583)
Testosterone deficiency [<300 ng/dL; no. (%)]	4/11 (36)	12/25 (48)
Nadir PRL [ng/mL; median (range)]	6.6 (0.1–17.1)	5.5 (0.3–1427)
Normal PRL [<15 ng/mL; no. (%)]	10/12 (83)	27/34 (79)
PRL decrease [median % (range)][a]	91.1 (81.7–99.9)	99.8 (81.3–99.9)

[a] $P < 0.01$.

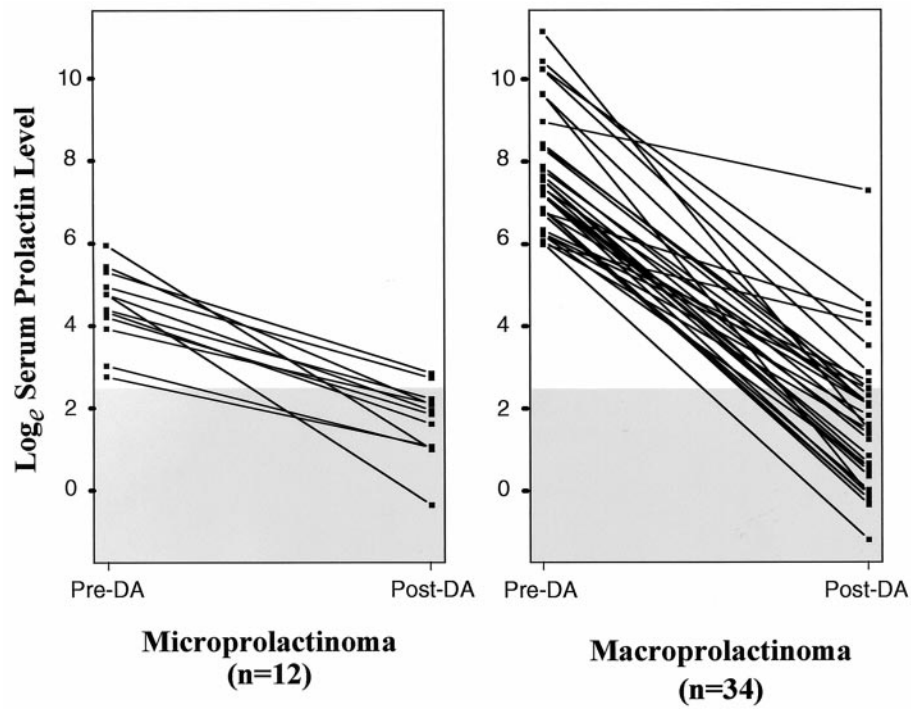

FIG. 1. Serum PRL levels at baseline and after DA administration in men with microprolactinomas and macroprolactinomas. PRL levels are displayed as $\log_e$ values. The *shaded area* represents the normal range for serum PRL levels (<15 ng/mL).

TABLE 3. PRL responses to different dopamine agonists in patients with microprolactinomas and macroprolactinomas: response rate and percentage of patients achieving a normal serum PRL (<15 ng/mL)

Dopamine agonist	Microprolactinomas			Macroprolactinomas		
	n	Response rate (%)	Dose [median (range)]	n	Response rate (%)	Dose [median (range)]
Bromocriptine	7	86	3.8 (1.3–7.5)	20	80	10 (3.8–35)
Cabergoline	3	100	1.5 (1.0–12.0)	10	90	2.3 (0.5–5)
Quinagolide	1	0	0.3	3	67	0.2 (0.1–.8)
Pergolide	1	100	2.5	0		
Untreated	0			1	0	

Dose, milligrams per day for bromocriptine, quinagolide, and pergolide, and milligrams per week for cabergoline.

normalization of PRL compared to 79% (95% confidence interval, 62.1, 91.3%) of men with macroprolactinomas (P = NS). As shown in Fig. 1 and Table 2, there was a significantly larger decrease in PRL levels in patients with macroprolactinomas *vs.* microadenomas during follow-up. Based on serial radiological reports, pituitary scans of 1 of 6 (17%) subjects with a microprolactinoma showed no evidence of residual tumor. In macroprolactinoma patients, there was a reduction in tumor size to less than 1 cm in 4 of 27 (15%), and no evidence of residual tumor in 5 of 27 (19%). No patient had evidence of an increase in tumor size during therapy.

During follow-up, men with macroprolactinomas (22%) continued to experience more headaches than men with microprolactinomas (0%; $P < 0.01$; Table 2). A comparable number of subjects in the 2 groups reported diminished libido, and impotence (P = NS). Nadir serum total testosterone levels were comparable in patients with macroprolactinomas *vs.* those with microprolactinomas (P = NS), and there was no significant difference in the prevalence of testosterone deficiency between the two groups (P = NS). We considered whether age correlated with testosterone deficiency, thus requiring adjustment, in the comparison of testosterone levels by performing Wilcoxon's rank sum test for differences in distribution between the ages of testosterone deficient and eugonadal men. At baseline, patients with microadenomas who were testosterone deficient tended to be older (median, 59 yr; range, 15.5–71.9 yr) than those who were eugonadal (median, 32.3 yr; range, 26.7–50 yr), but the difference was not statistically significant (P = NS). At baseline, patients with macroadenomas who were testosterone deficient were approximately the same age (median, 44.2 yr; range, 19.3–73.5 yr) as those who were eugonadal (median, 36.6 yr; range, 20.1–53 yr). Similarly, there was no significant difference in age between men who normalized testosterone levels during treatment with DA in either patients with micro- or macroadenomas (P = NS). Therefore, adjustment for age in the comparison of testosterone deficiency between the groups was not required. No patient with a microprolactinoma required exogenous testosterone therapy, in contrast to 33% of men with a macroprolactinoma. Of 8 of 11 (74%) men in the microprolactinoma group with testosterone deficiency at baseline, 4 of 11 (36%) remained testosterone deficient at follow-up (P = NS compared to baseline). Of 25 of 27 (93%) men with macroprolactinomas and testosterone deficiency at

baseline, 12 of 25 (48%) remained testosterone deficient at follow-up, including 4 men with serum testosterone levels below 300 ng/dL and 9 receiving testosterone replacement therapy ($P < 0.001$ compared to baseline). During the evaluation of the pituitary function at follow-up, patients with microprolactinomas did not require thyroid or glucocorticoid hormone replacement therapy. In contrast, a subset of macroprolactinoma patients required thyroid (n = 12) and/or glucocorticoid (n = 3) replacement therapy.

PRL responses to the different DA are shown in Table 3. The majority of patients in both groups were treated with bromocriptine, and a comparable number achieved normalization of PRL (<15.0 ng/mL) in the micro- *vs.* macroprolactinoma group (86% *vs.* 80%; P = NS). Similarly, a comparable number of patients with micro- *vs.* macroprolactinomas achieved PRL normalization with cabergoline therapy. The response rates for bromocriptine and cabergoline were also similar in both groups. One patient with macroprolactinoma was prescribed a DA, but was noncompliant with medication.

Discussion

We performed a retrospective study of 46 men with microprolactinomas and macroprolactinomas treated with medical therapy alone to assess clinical characteristics and response to DA administration. DA therapy had similar efficacy in normalizing PRL levels in men with microprolactinomas and those with macroprolactinomas.

We compared clinical characteristics in men with these pituitary tumors. There was no significant difference in the age of presentation in men with microprolactinomas *vs.* macroprolactinomas in our series. In a previous report of 13 patients with microprolactinomas and 38 with macroprolactinomas, a mean age of 42 ± 2.2 yr (range, 17–81 yr) at diagnosis was reported (7). In a series by Walsh *et al.* (8) of 8 patients with no demonstrable tumor, 8 with microprolactinomas, and 37 with macroprolactinomas, a mean age of 41 yr (range, 19–75 yr) at diagnosis was reported. However, neither study reported mean age characteristics for the microprolactinoma *vs.* macroprolactinoma subgroups. We found, as expected, that headache was the most frequent chief complaint for patients with macroprolactinomas, but not in patients with microprolactinomas. A lack of correlation between tumor size and duration of symptoms has been indicated in previous studies (5, 9). Our findings suggest that headaches are more frequent in subjects with macroprolactinomas. Recently, it has been suggested that prolactinomas have more aggressive growth characteristics in men compared to women. For example, in a study of 45 men and 51 women with prolactinomas, prolactinomas were significantly larger in men for all ages (5). In this study, giant prolactinomas and a PRL-secreting carcinoma were only seen in men. Colao *et al.* (10) investigated prolactinomas in children and reported that 8 of 9 (89%) boys *vs.* 7 of 17 (41%) girls had macroprolactinomas at diagnosis. Additionally, markers of cellular proliferation, including Ki-67 and proliferating cell nuclear antigen, are higher in prolactinomas from men (4, 5). Therefore, gender-related factors may also affect the rate of tumor growth. In some men, failure to detect sexual dysfunction may lead to a delay in diagnosis of a prolactinoma, resulting in a larger tumor size at diagnosis.

In our study the majority of microprolactinoma patients presented with complaints of symptoms of sexual dysfunction. However, symptoms of mass effect most commonly prompted macroprolactinoma patients to seek medical attention. The prevalence of diminished libido and/or impotence was 78–100% in both groups. These findings are consistent with a reported prevalence of sexual dysfunction from 76–95% in prior series. (1, 5, 7–9, 11). In both men and women with prolactinomas, serum PRL correlates with tumor size (5, 9). In our series, the higher serum PRL level was accompanied by a lower serum total testosterone level in the macroprolactinoma patients. Therefore, although serum testosterone levels are lower in men with macroprolactinomas, complaints of sexual dysfunction are similar to those in men with microprolactinomas.

A similar percentage of patients with microprolactinomas and macroprolactinomas received bromocriptine (58% *vs.* 59%) and cabergoline (25% *vs.* 29%) as medical therapy, although macroprolactinoma patients were receiving higher doses of bromocriptine (median dose, 3.75 *vs.* 10 mg/day) and cabergoline (median dose, 1.5 *vs.* 2.25 mg/week). Surprisingly, a similar percentage of patients with microprolactinomas and macroprolactinomas achieved normalization of serum PRL. Although in 1 patient with a macroprolactinoma the follow-up visit occurred after 1 month, excluding this patient did not affect the results of the study. These data support the concept that for most male patients, DA therapy can achieve PRL normalization, regardless of tumor size. Berezin *et al.* (7) reported that administration of DA to 53 hyperprolactinemic men resulted in a normal PRL level in 49% of subjects. In this study comparison of response rates for PRL normalization with tumor size was not performed. In our study we cannot conclude that there is a difference in the need for sequential DA use between men with micro- *vs.* macroprolactinomas, although the relatively low numbers of subjects in each group may limit this analysis. In our study, 6 of 7 (86%) microprolactinoma patients taking bromocriptine and 3 of 3 (100%) patients taking cabergoline achieved a normal serum PRL level. Similarly, 9 of 10 (90%) patients with macroprolactinomas receiving cabergoline achieved a normal serum PRL level. Published series in patients with prolactinomas suggest that cabergoline is more effective than bromocriptine in normalizing serum PRL levels (12). Colao *et al.* (13) demonstrated that prolactinomas resistant to bromocriptine may respond to cabergoline. DeRosa *et al.* (3) noted more rapid reversal of hypogonadism in hyperprolactinemic males treated with cabergoline than in those treated with bromocriptine. Our data suggest that each of these medications is effective in normalizing PRL levels in such patients.

Successful lowering of PRL resulted in a normal serum testosterone level in 52% of patients with macroprolactinomas, whereas similar success in lowering serum PRL in microprolactinoma patients resulted in serum total testosterone normalization in 63% of cases. However, sexual dysfunction remained prevalent despite DA therapy. These findings illustrate the need for surveillance of sexual dysfunction symptoms in all male patients with prolactinomas.

After initiation of DA therapy, only 19% of macroprolactinoma patients reported visual field abnormalities. At follow-up, visual fields were examined in 16 patients compared to 30 patients at baseline. At presentation, the difference in

visual abnormalities between men with micro- *vs.* macroprolactinomas was statistically significant, whereas at follow-up this difference was not significant. These data are in concordance with previous published studies of patients with prolactinomas (14–16), and our statistical analysis showed that the smaller number or patients investigated at follow-up did not bias the results. An improvement in tumor size was noted in 17% *vs.* 33% of microprolactinoma and macroprolactinoma patients, respectively. In previous series, a higher rate of tumor shrinkage compared to our findings has been noted (8). However, data derived from our retrospective review were based on CT and MRI reports that were not systematically compared by 1 radiologist. Therefore, our study may underestimate the true prevalence of DA-induced tumor shrinkage.

A strength of our study was the comparison of male patients with microprolactinomas to those with macroprolactinomas in terms of presentation and response to medical therapy. Most other series failed to consider these two patient populations separately, whereas some used pituitary imaging techniques that were unable to distinguish microprolactinomas from macroprolactinomas (1, 11). Although there was a selection bias in studying only medically managed patients, an advantage of our series is that it enabled a comparison of outcomes in a large number of men with both micro- and macroprolactinomas without the confounding effects of surgery, radiation therapy, or multiple treatment modalities. However, because this selection bias was present among all patients, it permitted us to select a relatively homogeneous group of patients with prolactinomas that differed primarily in size. This facilitated an accurate comparison of patients with microprolactinoma to patients with macroprolactinoma. In conclusion, long-term follow-up of DA-treated men with prolactinomas shows an overall normalization of PRL levels in approximately 80% of patients, and PRL normalization is comparable in patients with microprolactinomas *vs.* those with macroprolactinomas.

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