# Chapter 11
# Prolactinomas in Men

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## Introduction

Although prolactinomas are the most common pituitary tumors, they arise much less frequently in men than in women [1–5]. Based on several recent epidemiological studies, the estimated prevalence of prolactin-secreting tumors is around 10–15/100,000 men (1 in 7000), while it is about fivefold higher in women (60–70/100,000 women or 1 in 1500) (Table 11.1) [6–10]. Likewise, reported standardized incidence ratios (SIR) of prolactinoma are 3–4/100,000/year in women but only 0.8–1/100,000/year in men [10, 11].

While most female PRL-secreting tumors (90%) are microadenomas, men harbor macroadenomas in up to three-quarters of the cases [12, 13], so that the prevalence of macroprolactinomas (8–10/100,000) is roughly similar in both sexes [14–16]. Autopsy studies have however revealed a similar high prevalence of silent prolactin-containing microadenomas in men and women [17, 18], thus indicating that prolactinomas are diagnosed much less frequently in men than in women. This might be related to a lower awareness of related symptoms in males (such as altered libido and erection disorders which are often attributed to other causes) and/or to a lower sensitivity of the gonadotropic axis to hyperprolactinemia in males. Altogether, there is very likely an underestimation of the true prevalence of male microadenomas.

Although rare, male prolactinomas which come to medical attention have several distinct features that will be reviewed in the present chapter.

**Disclosures:** The author has no conflict of interest regarding this publication.

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N. A. Tritos, A. Klibanski (eds.), *Prolactin Disorders*, Contemporary Endocrinology, https://doi.org/10.1007/978-3-030-11836-5_11

**Table 11.1** Estimated prevalence of prolactinoma in the whole population, in the male population only, and of macroprolactinoma in the male population, as calculated from several recent epidemiological European studies

| | Belgium (Liège) | UK (Banbury) | Malta (whole island) | Iceland (whole island) | Finland (Oulu) |
|---|---|---|---|---|---|
| Study population (number) | 71,972 | 81,149 | 400,000 | 321,857 | 245,000 |
| Nb of prolactinomas (% of all pit adenomas) | 45 (66%) | 36 (57%) | 146 (46%) | 188 (40%) | 84 (55%) |
| Prevalence of prolactinomas | $63/10^5$ | $44/10^5$ | $35/10^5$ | $54/10^5$ | $63/10^5$ |
| Nb of prolactinomas in males (% of total) | 9 (20%) | 4 (11%) | 27 (19%) | 47 (25%) | 16 (19%) |
| Prevalence of prolactinomas in males | $18/10^5$ | $10/10^5$ | $13/10^5$ | $13/10^5$ | $13/10^5$ |
| Nb of macroprolactinomas in males (%) | 5 (56%) | NA | 17 (63%) | 30 (65%) | 12 (75%) |
| Prevalence of macroprolactinomas in males | $10/10^5$ | NA | $8/10^5$ | $8/10^5$ | $10/10^5$ |
| Reference | [6] | [7] | [8] | [9] | [10] |

*Nb* number, *pit* pituitary

## General Characteristics of Prolactinomas in Males

Differences in the general characteristics of prolactinomas between genders have been examined in several studies [16, 19–26], and some of the main data are summarized in Table 11.2. As already mentioned, the ratio between PRL-secreting microadenomas and macroadenomas is about 1:3 in males, whereas it is inverted (9:1) in females. This is also well illustrated in Fig. 11.1a, which shows the total numbers of men and women harboring microprolactinomas, macroprolactinomas, and giant prolactinomas (defined as tumors with a diameter ≥40 mm) in our own cohort of 490 patients diagnosed and followed in our institution for a 20-year period (July 1997–June 2017; *our unpublished data*). Also, the mean or median age at diagnosis is usually greater by 10 years in men than in women [7, 9, 10, 16, 19, 21–26] (Table 11.2 and Fig. 11.1b), likely reflecting a lower clinical alert threshold for diagnosis and not necessarily a later occurrence of the tumor in the male gender.

Not only are macroprolactinomas more frequent in men but they are also larger, more frequently invasive, and more often aggressive than in women [19, 22–27] (Table 11.2 and Fig. 11.2a). This larger tumor size in men has been for a long time attributed to a greater delay in diagnosis [14, 28]. Though this factor may indeed contribute to prolonged asymptomatic expansion of pituitary macroprolactinomas in men, important gender-related differences in tumor behavior have been now well established.

Higher rates of proliferation markers, such as the Ki-67 labeling index or the mitotic count, are found in surgically resected macroadenomas from males compared to similar tumors from females [19, 22–25]. Also, according to the prognos-

**Table 11.2** Comparison of the main characteristics of prolactinomas at diagnosis between men and women

| | Delgrange et al. [19] | | Colao et al. [20] | | Papegaey et al. [21][a] | | Khare et al. [16][a] | |
|---|---|---|---|---|---|---|---|---|
| | Males | Females | Males | Females | Males | Females | Males | Females |
| Reference | (*n* = 45) | (*n* = 51) | (*n* = 74) | (*n* = 130) | (*n* = 135) | (*n* = 125) | (*n* = 44) | (*n* = 56) |
| Age (years) | | | | | | | | |
| Mean ± SD | 42 ± 2 | 28 ± 1 | 35 ± 14 | 32 ± 12 | 42 ± 19 | 31 ± 15 | 35 ± 10 | 30 ± 10 |
| Range | [17–73] | [16–66] | NA | NA | [14–79] | [11–83] | [18–68] | [15–59] |
| Prolactin (μg/L) | | | | | | | | |
| Mean ± SD | 2789 ± 573 | 292 ± 7 | 188 ± 52 (m) | 135 ± 60 (m) | 3100 ± 5472 | 934 ± 2305 | 7927 ± 16,748 | 3094 ± 6863 |
| | | | 2848 ± 2954 (M) | 1132 ± 2351 (M) | | | | |
| Range | [62–16,550] | [36–2080] | | | [6–38,000] | [25–20,000] | [239–90,000] | [201–43,165] |
| Tumor diameter(mm) | | | | | | | | |
| Mean ± SD | 26 ± 2 | 10 ± 1 | 8 ± 1 (m) | 7 ± 2 (m) | 28 ± 13 | 19 ± 13 | 39 ± 15 | 25 ± 15 |
| | | | 26 ± 12 (M) | 17 ± 7 (M) | | | | |
| Range | NA | NA | | | [10–67] | [10–110] | [13–78] | [10–72] |
| Micro-/macroadenomas | 5/40 | 36/15 | 16/58 | 81/49 | 0/135 | 0/125 | 0/44 | 0/56 |
| Invasive macroadenomas (%) | 21/40 (53%) | 4/15 (27%) | NA | NA | 67/135 (50%) | 32/125 (26%) | 35/44 (80%) | 15/56 (27%) |
| Giant adenomas (%) | 8 (18%) | 0 (0%) | NA | NA | NA | NA | 18 (41%) | 7 (13%) |
| Hypogonadism (%) | 40 (89%) | 50 (98%) | 62 (84%) | 110 (85%) | NA | NA | 32 (76%) | 54 (96%) |
| Visual impairment (%) | 19 (42%) | NA | 28 (38%) | 18 (14%) | 51 (38%) | 17 (14%) | 17 (39%) | 7 (13%) |

*m* microadenomas, *M* macroadenomas, *NA* information not available

[a]These studies included only macroprolactinomas

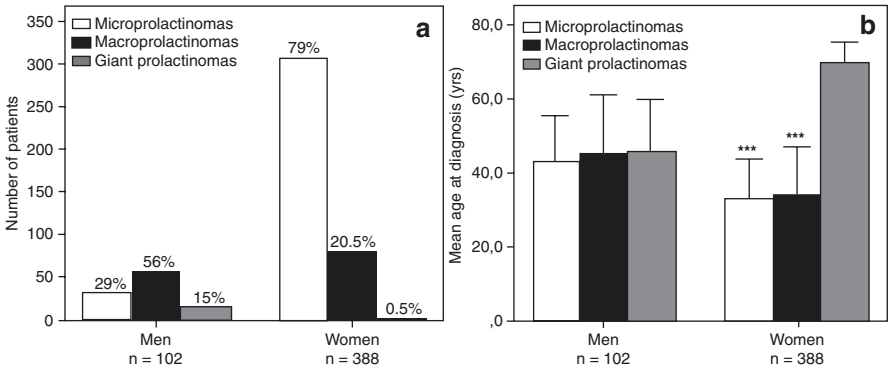


**Fig. 11.1** (**a**) Total numbers and percentages and (**b**) mean age at diagnosis (+ standard deviation) in 102 men and 388 women harboring either a microprolactinoma (white bars), a macroprolactinoma (black bars), or a giant prolactinoma (defined as a tumor with a diameter ≥40 mm and a prolactin concentration ≥1000 μg/L; gray bars). Data are calculated from our own cohort of 490 patients diagnosed and followed for a prolactinoma in our institution during a 20-year period (July 1997–June 2017; *unpublished data*). ***: $P < 0.001$ vs males with the same tumor size category

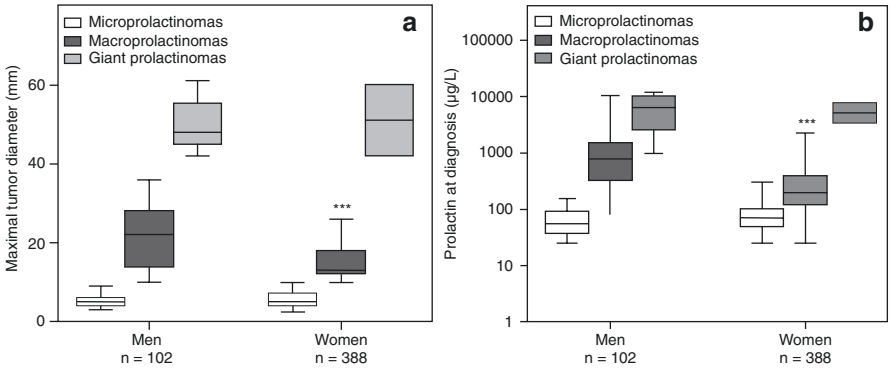


**Fig. 11.2** (**a**) Maximal tumor diameter (in mm) and (**b**) prolactin concentrations at diagnosis (in μg/L) in 102 men and 388 women harboring either a microprolactinoma (white bars), a macroprolactinoma (black bars), or a giant prolactinoma (defined as a tumor with a diameter ≥40 mm and a prolactin concentration ≥1000 μg/L; gray bars). Data are calculated from our own cohort of 490 patients diagnosed and followed for a prolactinoma in our institution during a 20-year period (July 1997–June 2017; *unpublished data*). The box and whisker plots represent medians, interquartile ranges, and [P5–P95] intervals, respectively. ***: $P < 0.001$ vs males with the same tumor size category

tic clinicopathological classification proposed by Trouillas et al. [29], men have higher-grade (2b and 3) tumors than women. For example, of the 64 malignant prolactinomas (grade 3 tumors) reported in the English literature between 1981 and 2015, 40 were observed in men and 24 in women [5].

The preponderance of large tumors in males is also largely independent of age [19], and a higher prevalence of macroprolactinomas is seen in boys compared to

girls [30–32]. As shown in Fig. 11.1a, giant prolactinomas are mainly observed among males [33, 34], being found in boys as young as 7 years old [35, 36], and the median age at diagnosis of these very large and invasive PRL tumors is greater by almost 10 years in women compared to men [37]. Finally, most women of childbearing age still exhibit small intrasellar tumors, even after a long duration of symptoms [19], and studies of the natural history of such microadenomas have shown little or no evolution [5]. It is worth mentioning here that the natural history of microprolactinomas is unknown in men, probably because of their rare discovery and the fear of a more aggressive course of disease leading to early treatment. However, they may also remain small, as a long history of impotence is still consistent with the finding of a small PRL-secreting microadenoma [19].

Regarding prolactin concentrations at diagnosis, significantly higher levels are constantly observed in men as compared to women (Table 11.2). However, while Colao and colleagues found higher male PRL concentrations for both micro- and macroadenomas [20], we could only observe such a sex difference in the case of macroprolactinomas ([19]; Fig. 11.2b). Interestingly, higher prolactin levels in male macroprolactinomas are not only related to a larger tumor size but also to a higher secretion rate per tumoral size unit, at least for tumor diameters between 10 and 25 mm, as illustrated in Fig. 11.3. This sex difference in tumoral PRL secretion rate might partly be due to the presence of cystic and/or hemorrhagic changes which seem to occur more frequently in female macroprolactinomas [38–40].

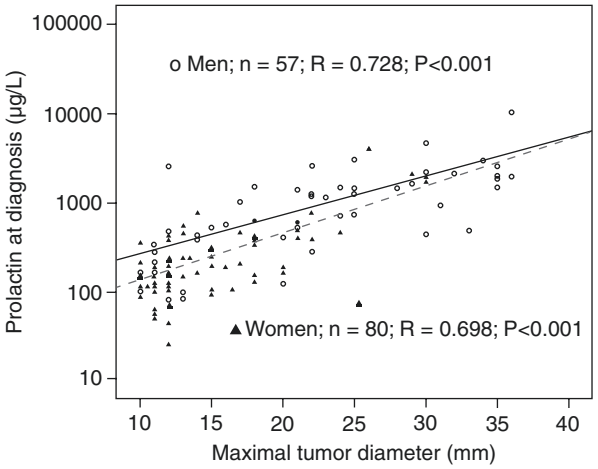


**Fig. 11.3** Correlations between maximal tumor diameter (in mm) and prolactin concentration (in µg/L on a log scale) in men (open circles and solid regression line; $n = 57$) and in women (close triangles and dashed regression line; $n = 80$) with a prolactinoma size between 10 and 40 mm. Data are calculated from a cohort of 137 patients diagnosed and followed for a macroprolactinoma in our institution during a 20-year period (July 1997–June 2017; *unpublished data*) and with both parameters available at diagnosis

### *Why Are Male Prolactinomas Different from Female Prolactinomas?*

The reasons for a more aggressive course of prolactinomas in men remain poorly understood. Some clinical data indeed suggest that estrogens could halt PRL tumor progression. A bimodal age distribution of giant prolactinomas is observed in women, with a very low occurrence in childbearing-aged women [37, 41–43]. The proliferative activity of PRL tumors is higher in men and in women older than 40 compared to young women [19, 23]. Delgrange and colleagues also reported recently that a lower expression of estrogen receptor alpha (ERα) is more frequently observed in male prolactinomas and is associated with higher proliferation rates, resistance to dopamine agonists, and progression despite multimodal therapy [26]. They made the hypothesis that, as observed in breast cancer, the loss of ERα might be a sign of tumor dedifferentiation and poorer prognosis.

These observations may seem counterintuitive, as estrogens are known to promote pituitary tumorigenesis and angiogenesis, via induction of pituitary tumor transforming gene (PTTG), in turn leading to increased production in the pituitary gland of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) [44]. In fact, estrogens appear to differentially influence PRL cell proliferation and PRL secretion [45]. Thus, although there is some evidence of estrogen stimulation of PRL secretion by prolactinoma cells in pregnant women [46] and men [47], no association has been reported between estrogen exposure and development or growth of prolactinoma in women treated with oral contraceptives [48] or in male-to-female transsexuals [49].

The mechanisms by which a higher expression of ERα in female prolactinomas is associated with an inhibition of tumor growth are still unknown. They might involve estrogen-mediated activation of dopaminergic pathways and subsequent dopamine-induced antiproliferative and pro-apoptotic effects [50]. Transforming growth factor-beta1 (TGF-b1) could be another potential player, as it is a known inhibitor of lactotroph proliferation and it is positively regulated by dopamine and negatively by estradiol. Pituitary expression of active TGF-b1 and of putative TGF-b1 activators is higher in normal male mice compared to female mice, and it is postulated that this higher expression TGF-b1 system in male animals could protect them against the development of prolactin tumors [51, 52]. This protection could be lost by down-regulation of the TGF-b1 system in the human male prolactinomas. However, such a mechanism is purely speculative at this time and remains yet to be demonstrated.

## Clinical Presentation

Striking differences also exist in the clinical presentation of prolactinoma between sexes. While most women with a prolactinoma come to medical attention during their reproductive period because of oligomenorrhea or amenorrhea, infertility, and/

or galactorrhea [4, 5, 53, 54], more than half of men present initially with symptoms of mass effects [12, 16, 19–21]. Reviewing 16 studies involving 444 males, Gillam et al. reported the presence of visual field defects in 37%, hypopituitarism in 34%, and headaches in 29% [4]. These figures are much lower in women, as illustrated in Table 11.2 for the occurrence of visual field defects.

Although present in the majority of men with a prolactinoma [19, 55–57], symptoms of male hypogonadism, such as loss of libido, erectile dysfunction, gynecomastia, altered sperm features, and infertility or osteopenia, are often unrecognized for a long period of time, or they are attributed to other causes such as age, drugs, or depression. Thus, endocrine symptoms are less frequently the reason to seek medical advice for men with a prolactinoma [5]. On the other hand, galactorrhea is rare in men, as it requires both a fall in testosterone levels and an estrogen excess which is not the rule in case of hyperprolactinemia [4, 5].

Interestingly, the male reproductive axis also seems to be more resistant to chronic prolactin excess than the female axis. Indeed, while in women menstrual dysfunction or galactorrhea is commonly seen with minimal PRL elevations [5], normal testosterone levels may still be observed in many patients with mild hyperprolactinemia [58] and in 20–30% of patients with a micro- or a macroprolactinoma [13, 19, 59, 60]. Likewise, semen quality is significantly altered in only half of men with prolactinoma, and nearly all of them retain some sperm production capacity [56, 57]. The reasons for this differential sensitivity of the male reproductive axis are not fully elucidated. These patients with an apparently preserved gonadal function have usually smaller and less aggressive tumors causing no permanent damage to the gonadotrophs. Moreover, when these men are treated effectively with a dopamine agonist, testosterone levels increase further to higher concentrations within the normal range, and this is often associated with an improvement of sexual function [59, 60], suggesting that baseline testosterone concentrations were likely lower than the optimal values for those individuals.

Other symptoms and signs may be related to hypopituitarism (apart from hypogonadism), which is exceptional in the case of microadenomas, but present in about 30–50% of men with a macroprolactinoma [13, 20, 54, 61, 62]. Central hypothyroidism (present in 18–41%) seems to be more prevalent than ACTH deficiency (12–33%), all deficits are more prevalent among patients with larger adenomas, and recovery of normal hormonal axes occurs in only half of the cases [61]. The exact prevalence of growth hormone (GH) deficiency is not known but likely higher than those of TSH and ACTH deficits. Limited data indicate that GH secretion may recover following successful medical treatment of hyperprolactinemia in most but not all subjects with a macroprolactinoma [63]. In any case, all men with a macroprolactinoma should be carefully evaluated for possible deficits in pituitary function.

Quite intriguingly, two recent retrospective studies have demonstrated an increased risk for cardiovascular disease (CVD) in men but not in women with hyperprolactinemia. The first study included individuals with hyperprolactinemia irrespective of its primary etiology, and the authors reported a higher risk for cardiovascular and all-cause mortality in men as compared to women [64]. In the second

population-based cohort study of more than 12,000 subjects, incident CVD was increased only in men with prolactinoma, with an incidence risk ratio of 1.72 over a 6-year period [65]. Long-standing hyperprolactinemia and its metabolic consequences, such as concomitant insulin resistance and hypercoagulable state, as well as hypopituitarism and its management, were proposed as the underlying mechanisms, without however a clear explanation for sex specificity, except for the known differences in tumor size and invasiveness between men and women. Further studies are clearly needed to confirm and better characterize these findings.

## Diagnosis

The diagnosis of prolactinoma in men should rely on the same criteria as in women [4, 5, 53], namely, (i) the repeated observation of elevated prolactin concentrations, (ii) exclusion of other causes that might account entirely for hyperprolactinemia (such as macroprolactin), (iii) unequivocal finding of a pituitary adenoma, and (iv) exclusion of a mixed GH-PRL adenoma with acromegaly. Noteworthily, prolactin concentrations (2–15 μg/L) are lower in healthy men than in normal women, and this is also true for most causes of hyperprolactinemia other than prolactinomas. As an example, the maximal level of hyperprolactinemia related to a pituitary stalk effect caused by a non-lactotrope tumor of the sellar region is lower in men than in women [66].

In men as in women, prolactin levels correlate well with prolactinoma size, especially in the case of macroprolactinomas (Fig. 11.3). Most microprolactinomas have levels between 50 and 150 μg/L [4, 5]. Virtually all macroprolactinomas have levels above 100 μg/l, and patients with large adenomas have PRL levels well above 250 μg/l. Nevertheless, it is always wise to rule out one of the many other disorders which may be responsible for hyperprolactinemia, before making the diagnosis of prolactinoma, and this in men as in women [5].

Regarding magnetic resonance imaging (MRI) findings, some gender differences have been reported between male and female prolactinomas [67]. In addition to being smaller and less frequently invasive, most prolactinomas in women appear to be hyperintense on T2-weighted sequences, while the presentation in men is more heterogeneous. Most male PRL adenomas are iso-intense on T2 images, and 15% of them have a peculiar low T2 signal intensity which might correspond to the presence of spherical amyloid deposits.

As reviewed elsewhere [33], the diagnosis of a giant prolactinoma may sometimes be very challenging and delayed in some men, as the mode of presentation may be atypical for a pituitary tumor while more specific symptoms are neglected. In addition, in such cases, patients with extremely high PRL levels may appear to have only moderate PRL elevation, due to the so-called hook effect [5, 33], and the prolactinoma may be misclassified as a clinically nonfunctioning macroadenoma.

## Treatment

A similar therapeutic strategy should be used for male and female prolactinomas. Medical management with dopamine agonists (DA) is considered as the first-line therapy as it is highly effective and safe in men as in women, including those men bearing large or even giant macroprolactinomas [5, 53]. Transsphenoidal surgery should be reserved for patients who are either intolerant or resistant to DAs [68], and most of these operated males will still require a DA to control prolactin hypersecretion [54]. Radiation therapy or radiosurgery should rarely be employed and only to control the growth of aggressive tumors which do not respond to conventional treatment [69].

### *Dopamine Agonists*

Few retrospective studies have carefully compared the hormonal and tumoral responses to dopamine agonists between men and women with a prolactinoma [16, 19–21], and discordant results have been reported (Table 11.3). While Delgrange et al. reported a significantly better response to bromocriptine in women than in men with resistance rates of 5% and 30%, respectively [19], other authors did not find any sex difference in the sensitivity to cabergoline, when tumors were matched for size [16, 20, 21]. Likewise, Verhelst et al. showed that male patients were less likely to achieve normal PRL levels on cabergoline treatment than females [70]. However, when considering the fact that more males had a macroprolactinoma, gender had no longer an independent influence on the hormonal control rate. Although no direct comparison was made with a female population, a very good efficacy of medical treatment was also reported for male prolactinomas by Pinzone et al. [12] and by Iglesias et al. [13], with little difference in the hormonal response rates (65–80%) between micro- and macroprolactinomas.

These results must be challenged against the observations that male gender is usually prevalent among patients exhibiting full resistance to cabergoline [19, 26, 27, 71], that most prolactin-secreting carcinomas arise in men [5], that the dose of cabergoline required to control hyperprolactinemia is often higher in men than in women with a macroprolactinoma [16, 20, 26, 70], and that in at least one study, male gender was associated with resistance to cabergoline, independent of tumor size or invasiveness [27]. Altogether, it seems fair to say that based on current knowledge, prolactinomas are more resistant to medical treatment in men than in women but that this difference is mostly, but perhaps not entirely, due to the greater proportion of large and invasive tumors in the male gender.

Importantly, restoring normal prolactin concentrations with a dopamine agonist allows the restoration of normal gonadal function (including normal semen quality) in most men with prolactinoma [56, 57, 60] and preserves other pituitary functions much better than do surgery or radiotherapy [13, 54]. Symptomatic hypogonadism

**Table 11.3** Comparison of the response to dopamine agonists between men and women with prolactinoma

| | Delgrange et al. [19] | | Colao et al. [20] | | Papegaey et al. [21][a] | | Khare et al. [16][a] | |
|---|---|---|---|---|---|---|---|---|
| | Males | Females | Males | Females | Males | Females | Males | Females |
| Reference | ($n = 45$) | ($n = 51$) | ($n = 74$) | ($n = 130$) | ($n = 135$) | ($n = 125$) | ($n = 44$) | ($n = 56$) |
| Micro-/macroadenomas | 5/40 | 36/15 | 16/58 | 81/49 | 0/135 | 0/125 | 0/44 | 0/56 |
| Type of DA | BRC | BRC | CAB | CAB | CAB | CAB | CAB | CAB |
| Median dose of DA (mg/week) | NA | NA | 1.0 (m) | 1.0 (m) | NA | NA | 1.5 | 1.0 |
| | | | 1.5 (M) | 1.0 (M) | | | | |
| Nb of patients with PRL normalization (%) | 26/37 (70%) | 35/37** (95%) | 51/74 (69%) | 91/130 (70%) | 73/96[b] (76%) | 62/83[b] (75%) | 22/34 (65%) | 39/54 (72%) |
| Maximal tumor decrease (%; mean ± SD) | NA | NA | 38±29 (m) | 44±31 (m) | NA | NA | 51±22 | 42±24 |
| | | | 52±23 (M) | 45±25 (M) | | | | |

*m* microadenomas, *M* macroadenomas, *NA* information not available

[a]These studies included only macroprolactinomas

[b]These data represent the numbers of patients normalizing prolactin with a dose of cabergoline ≤2.0 mg/week

may however persist in a significant subset of these patients, even when PRL levels are normalized [5, 12, 14], and testosterone supplementation is therefore often required. This testosterone treatment may sometimes be associated with a secondary elevation in PRL levels and with resistance to dopamine agonists. In such cases, combination of a dopamine agonist and an aromatase inhibitor may be helpful [47]. Medical treatment also quickly alleviates acute symptoms due to compression of neighboring structures by very large and invasive prolactinomas in men [5, 33]. Thus, dopamine agonists remain the first therapeutic option also in patients with large or giant prolactinomas, resulting in marked and rapid reductions of prolactin concentrations and tumor size in 80% of cases. Interestingly enough, the proportion of men is similar (around 75%) between good responders and non-responders [33].

Another final gender difference regarding medical treatment concerns the rate of remission observed after withdrawal of dopamine agonists. Based on the latest Endocrine Society guidelines [53], therapy with dopamine agonists might be discontinued in prolactinoma patients who have been treated for at least 2 years, who have normal prolactin concentrations with a low dose of the dopamine agonist, and who have demonstrated a clear reduction of tumor size on treatment (ideally tumor disappearance on MRI). Using such criteria to support the decision of drug withdrawal, Colao et al. reported that the recurrence rate was markedly higher in men than in women (63% vs 32%, respectively) [72]. This finding was however not confirmed in other studies, which usually identified size of the tumor remnant and PRL nadir as the two main factors predicting long-term remission [73, 74]. Very recently, Texeira and colleagues [75] observed that DA withdrawal was in fact more frequently attempted in women (45/115, 39%) than in men with prolactinoma (5/27, 19%) but that once the conditions for withdrawal were met, the recurrence rate was similar between sexes.

## *Surgery*

Although not the primary treatment, transsphenoidal microsurgery may still be required for a number of men with prolactinomas, who are intolerant or resistant to any available dopamine agonist or who elect to undergo surgical excision of their adenoma [4, 5, 53]. Several studies including mixed cohorts of male and female patients did not demonstrate any influence of gender on the surgical outcome [76, 77]. Preoperative PRL level, tumor size, and extension are usually the main predictors of postoperative remission. Raverot et al. reported that persistently elevated prolactin levels after surgery were associated with male sex by univariate analysis, but not by multivariate analysis. Only invasion and pathological classification were independently associated with negative surgical outcome [78].

In specialized centers, the overall efficacy of pituitary surgery is reasonably good in men with prolactinoma (around 60%). Postoperative initial remission is clearly better for microprolactinomas (80–90%) than for macroprolactinomas (40–50%) [68, 76–80], and the remission rate is further dramatically reduced when the tumor is invasive, as it is often the case in males [24]. Moreover, relapse of hyperprolac-

tinemia is frequent, occurring in 20% of the initially cured patient's recurrences [5, 68]. Thus, in most cases, adjunctive medical treatment will still be required to control persistent postoperative hyperprolactinemia.

The treatment of aggressive and malignant prolactin-secreting tumors, which are fortunately rare but more prevalent in men than in women, will be discussed in a separate chapter.

## Conclusions

The prevalence of clinically significant prolactinomas is clearly lower in men than in women. However, male prolactin-secreting pituitary tumors have several distinct features that should raise medical interest. They are larger, more frequently invasive, and more often aggressive than in women, and these characteristics are largely due to sex differences in tumor behavior. Significantly higher prolactin concentrations are observed in men as compared to women, especially in the case of macroprolactinoma. Striking sex differences also exist in the clinical presentation of prolactinoma. Most women will present with oligomenorrhea, infertility, and/or galactorrhea, while more than half of men initially complain from symptoms of mass effects. Male hypogonadism is often present but neglected, and the male reproductive axis is also less sensitive to hyperprolactinemia than the female one.

The diagnosis of prolactinoma in men should rely on the same criteria as in women, and prolactin levels correlate well with prolactinoma size, especially in the case of macroprolactinoma, Likewise, a similar therapeutic strategy should be used for male and female prolactinomas. Medical management with dopamine agonists (DA) is highly effective and should always be considered as the first-line therapy, also in men bearing very large and compressive tumors. Transsphenoidal surgery should be reserved for patients who are either intolerant or resistant to dopamine agonists or who elect to undergo surgery. However, most male patients will still require a DA to control prolactin hypersecretion after surgery for a macroprolactinoma.

The reasons for a more aggressive course of prolactinomas in men remain poorly understood but might be related to differential and gender-related effects of estrogens on tumor growth and prolactin secretion. In any case, male prolactinomas offer a unique opportunity to further elucidate some mechanisms responsible for invasive and aggressive behavior of pituitary tumors.

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