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Prolactinomas in males: any differences?

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Abstract

Context Prolactinomas in men are usually large and invasive, presenting with signs and symptoms of hypogonadism and mass effects, including visual damage. Prolactin levels are high, associated with low testosterone, anemia, metabolic syndrome and if long-standing also osteoporosis.

Results Medical treatment with the dopamine agonist, cabergoline, became the preferred first-line treatment for male prolactinomas as well as for giant tumors, leading to prolactin normalization in ~ 80% of treated men, and tumor shrinkage, improved visual fields and recovery of hypogonadism in most patients. Multi-modal approach including surgery and occasionally radiotherapy together with a high-dose cabergoline is saved for resistant and invasive adenomas. Experimental treatments including temozolomide or pasireotide may improve clinical response in men harboring resistant prolactinomas.

Conclusions Compared to other pituitary adenomas, secreting and non-secreting, where pituitary surgery is the recommended first-line treatment, men with prolactinomas will usually respond to medical treatment with no need for any additional treatment.

Keywords Cabergoline · Dopamine agonist · Men · Prolactin · Prolactinoma

Introduction

Men with prolactinomas usually harbor macroadenomas, sometimes very large, which affect clinical presentation. Prolactinomas in men typically present with either features of hypogonadism, including erectile dysfunction, decreased libido, oligospermia, weakness and gynecomastia; and/or with complaints attributed to the mass effect, visual field damage, and headaches [1–3]. Galactorrhea is rare in men [4]. Apart from hypogonadism induced by hyperprolactinemia, other pituitary hormone deficiencies (mostly thyroid hormone and cortisol), may affect symptoms at presentation, especially in men with larger tumors [5]. A minority of men with large tumors may present with pituitary adenoma apoplexy [6].

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Hypogonadism

Increased prolactin concentration inhibits hypothalamic gonadotropin releasing hormone and pituitary LH and FSH secretion. Excessive prolactin levels might also have a direct negative effect on testicular tissue [7]. Symptoms directly related to hypogonadism are prevalent among men with prolactinomas, although normal testosterone are observed in some affected men, and should not exclude the diagnosis of prolactinoma in men [4].

Impaired bone density is a frequent consequence of long-term hyperprolactinemia associated with hypogonadism, and correlates with duration and severity of hypogonadism [8]. In a recent series of 44 men with prolactinomas, diagnosed at 22–78 years old, 27% had impaired bone mineral density at baseline, and 37% at last follow-up [9]. In addition, men with prolactinoma had higher rates of vertebral fractures compared to men with normal prolactin levels [37.5% vs. 7.9% respectively] regardless of testosterone levels [10].

In men with macroprolactinomas mild anemia is common. It is associated with hypogonadism, and usually improves following successful treatment and normalization of prolactin and testosterone, a recognized growth factor for bone marrow erythropoiesis [11, 12].

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Hypogonadal men are at higher risk for developing metabolic syndrome, and testosterone replacement may improve several metabolic parameters, including waist circumference, body mass index (BMI), lipids profile, and glucose metabolism [13]. Weight gain and increased BMI are frequently associated with prolactinomas regardless of tumor involvement of the hypothalamus or pituitary function. In a series published in 1998, weight loss (mean change -8.3 ± 1.5 kg) was reported in 70% of a cohort of prolactinoma patients, and in 90% of male patients who normalized their prolactin levels [14]. A recent study comparing body fat content and distribution in men with newly diagnosed prolactinomas, normoprolactinemic men following treatment with dopamine agonists (DA), and matched controls, showed that men with untreated prolactinomas had higher body fat content [15]. This aligns with the observation that men with prolactinoma have increased cardiovascular risk [16].

Hypogonadism is not always recognized by male patients. Elderly patients with hyperprolactinemia and hypogonadism may become aware of their hypogonadism only following clinical improvement with medical treatment for their prolactinomas [17].

Men who do not normalize testosterone levels upon prolactin normalization may require testosterone replacement treatment. Factors that may influence hypogonadism persistence include baseline tumor size, prolactin and testosterone levels. Testosterone replacement therapy may be considered if eugonadism was not achieved after 3–6 months of continuous normoprolactinemia, especially if hypogonadal symptoms are evident. A potential risk is that testosterone aromatization into estrogen will stimulate proliferation and hyperplasia of lactotroph cells in the pituitary, inducing DA resistance [18]. Thus, testosterone target level should aspire to the mid-normal range. Short acting preparations (gel applicants or injectable) should be preferred over the long acting preparations, at least when treatment is initiated.

If pregnancy is desired, and not achieved after at least 6 months of normoprolactinemia while on DA, fertility treatment may be considered and referral to fertility specialist is advised.

Differences between men and women–reasoning

Prolactinomas in males are larger than in females, and associate with higher prolactin levels at diagnosis. Whereas women are diagnosed more often with micro-prolactinomas, macroprolactinomas and giant adenomas are frequently found in male patients. Prolactinomas in men are often rapidly growing and invasive tumors, compressing adjacent structures [19–21]. The 2017 World Health Organization Classification of pituitary tumors reflect those observations and notes that although the majority of prolactinomas are sparsely granulated, the more aggressive and resistant densely granulated tumors are mainly found in males [22].

A possible explanation for these differences is the delayed diagnosis in men. Females are diagnosed earlier through complaints of menstrual irregularities, galactorrhea, and infertility, while the less specific (and even embarrassing to some) presenting symptoms in men—decreased libido and other symptoms of hypogonadism—might be responsible for men seeking medical attention later. Larger adenomas can occasionally present with mass effect only, thus, possibly further delaying diagnosis. Nevertheless, this theory is not applicable to male microprolactinomas with indolent progression, presenting without significant growth.

Gender differences in the expression levels of galanin, vasoactive intestinal peptide (VIP), and estrogen receptors may account for the differences in tumor behavior in males and females [23, 24].

Gender may have an impact on the biologic activity of prolactinomas, with more aggressive behavior in men, as portrayed with higher Ki-67, cellular atypia, angiogeneic and proliferative features, and invasion in male prolactinomas [19, 20, 25, 26]. Data from small series implies that even within the group of resistant prolactinomas, men appear to have a more aggressive nature compared to females [20].

Treatment—response and side effects

The preferred mode of treatment for prolactinomas is medical treatment with DA. This is true for men harboring small or large adenomas, as well as localized and invasive ones.

It is already 50 years from the discovery of bromocriptine [27] and the introduction of long-term treatment with bromocriptine for women and men with prolactinomas [28]. Treatment with DAs, bromocriptine in the past and currently cabergoline, is effective in most male patients with prolactinoma in normalizing prolactin and reducing tumor size [2, 6, 29–32]. In a recent review, summarizing 12 published series of patients with macroprolactinomas treated with cabergoline (191/309 patients were men), prolactin normalized in 80% of the cases and tumor shrunk significantly in 87% of patients [33]. Improvement of visual field defects was depicted in 83% of patients with macroadenomas and visual damage. Thus, primary medical treatment with cabergoline can be safely recommended for patients with invasive adenomas and compromised vision.

We have summarized 15 cohorts of patients with prolactinomas treated during the past three decades, including 736 men treated medically mostly with cabergoline (86% of the cohort; Table 1); 85% of these harbored a macroadenoma, including giant adenomas. Mean prolactin level at diagnosis was 2491 ng/ml, and 73% presented with hypogonadism.

Table 1 Baseline characteristics and beneficial effects of medical treatment in men with prolactinomas

Author	Year	No. of men(m)	Mean Maximal Diameter (mm) *presented as volume	Macro-adenomas (%)	PRL - ng/ml	Age (years)	Hypogonadism	Dopamine agonist (CAB/BCP)	TSS	RT (%)	PRL Normalization (%)
Colao et al. [2]	2003	74(16)	M 26; m 8.0	78	M 2848; m 188	35	M 46/58; m 8/16	74/0			M 64%; m 86%
Tirosh et al. [5]	2015	81	30.4	100	7511	45	64/73	81/0	16/81		90%
Iglesias et al. [6]	2012	88 (15)	M 32; m 8;28 ± 16	83	NA	40	M 54/73; m 7/15	61	14/88	13/88	69%, M 65%; m 73%
Andereggen et al. [9]	2017	44 (8)	NA	82	M 3130; m 220	47	18/44	26/8	15/44		52%,M 47%; m 75%
Mazziotti et al. [10]	2011	32	NA	69	98	47	25/32	23/0			NA
Auriemma et al. [13]	2015	32	NA	78	2028	42	22/32	32/0			97%
Shimon et al. [17]	2019	28	16.3	61	1594	71	21/28	27/1			86%
Day et al. [25]	2010	40	33.6	95	4634	42	29/42	40/0	11/40		NA
Nishioka et al. [26]	2003	16	*15 ± 15 cm^3	NA	1946	37	NA	NA	16/16		NA
Bhansali et al. [29]	2010	15	*29 ± 8 cm^3	100	6249	32	NA	15/0			93%
Coalo et al. [30]	2004	51(10)	M 23; m 8	80	M 2019; m 182	33	M 30/41; m 5/10	51/0			M 76%; m 80%
Sibal et al. [31]	2002	35	NA	100	2817	NA	27/35	35/0			83%
Yarman et al. [32]	2012	22	29	100	1228	45	7/22	14/8			NA
Qu et al. [44]	2011	87	NA	79	975	38	68/87	NA/47	87/87		M 45%; m 83%
Dogansen et al. [46]	2019	92	26	NA	2066	43	80/92	92/0			NA
Total (15 cohorts)		736 (49)		85%	All 2491, m 194		511/700	CAB, N, 510–571	159		76%

Summary of 15 published cohorts of patients with long-term follow-up

m microprolactinomas, *M* macroprolactinoma

Trans-sphenoidal adenoma resection was performed in 159 patients, and 13 patients in one cohort underwent radiation treatment. Overall, 76% of the men normalized prolactin during follow-up. Data regarding microprolactinomas was available for 49 men; mean prolactin at presentation was 194 ng/ml, and prolactin normalized in 34 (70%) men.

Resistance to DA treatment was defined differently in various publications, usually as failure to normalized prolactin, despite continuous cabergoline dose ≥ 2 mg/week or more than 3.5 mg/week, and/or inadequate adenoma shrinkage of > 50% of baseline volume. Others relied on clinical parameters such as absence of ovulation in women despite treatment [34].

Tumors resistant to cabergoline treatment are often macroadenomas showing aggressive features, although resistant microprolactimomas also exist. Variations in time from initiating treatment with DA to prolactin suppression might reflect D2 dopamine receptor expression level on tumor cells, ratio of the dopamine receptor isoforms, or activity of Gi/Go proteins coupled to adenylate cyclase in tumor lactotroph cells [35].

In resistant tumors, adding somatostatin analogues such as octreotide LAR, or the novel somatostatin ligand pasireotide, may occasionally improve response [36–38]. Temozolomide, an oral alkylating agent, might be an option for clinically aggressive and resistant giant prolactinomas [39, 40], and for prolactin-cell carcinomas. Importantly, prolactinomas initially responding to DA rarely transform later to metastatic prolactin-secreting carcinoma, even after a long-standing period of prolactin and tumor control [41].

Surgical treatment for men has a low success rate, ranging in different series from 0 to 83%, depending on tumor size, invasiveness, and prolactin levels [9, 25, 42–44]. When assessing the data separately for microadenomas and macroadenomas in both men and women, surgical remission rates varied from 38 to 100% for microadenomas and up to 45% for macroadenomas [21]. Thus, in macroprolactinomas, the normalization rates of prolactin levels are much lower, especially in invasive tumors. Moreover, hypeprolactinemia may recur after initial hormonal control following surgery. Previous exposure to DA treatment may induce intratumoral fibrotic changes that prevent achieving post-operative hormonal remission, and these patients are more likely to develop pituitary dysfunction [45].

A multi-modal approach including surgery and radiotherapy together with continuous medical treatment is reserved for resistant, invasive, or visual threatening tumors, and for men who develop severe adverse effects to DA treatment.

A rare complication of DA treatment in men is impulse control disorder, also called "Dopa-testotoxicosis", comprising of pathological behaviors such as gambling, hypersexuality, compulsive shopping, compulsive eating, and impulsivity. In a recently published series from Turkey, Dopa-testotoxicosis was more common in male patients with a history of gambling, smoking, or alcohol use [46]. Increases in testosterone levels, after a prolonged hypogonadal state, combined with a reward pathway stimulation by DA treatment, might be responsible for this rare and disturbing phenomenon [47].

Cabergoline is also reported to cause valvulopathy in Parkinson's disease patients, treated with high doses of DA (cumulative dose of more than 4000 mg of cabergoline) [48]. A proposed mechanism for the DA associated valvulopathy is through stimulation of the 5-Hydroxytryptamine (5-HT) receptor, causing fibroblast proliferation [48]. Although patients with prolactinomas are given lower doses of DA than those given to patients with Parkinson's disease, men with prolactinomas may occasionally require higher doses of DA than women. Yet, in retrospective series, there was no association of high dose DAs with valvulopathy [32, 48]. Decisions regarding follow-up with echocardiography in men treated with high dose cabergoline should be left to the physicians' discretion.

Giant tumors

Giant prolactinomas, measuring more than 40 mm in maximal diameter and presenting with very high prolactin levels (≥ 1000 ng/ml), are rare. Giant tumors are usually diagnosed in men, with a reported male to female ratio of approximately 9:1 [39].

Presenting symptoms are often related to mass effects including headache and visual field defects, in addition to symptoms of hypogonadism and hypopytuitarism. Massive extrasellar extension, reported in many cases of giant prolactinomas [39], might account for various unique neurologic symptoms including epilepsy, reversible dementia, or obstructive hydrocephalus [49].

Despite their aggressiveness, these tumors are mostly benign and respond well to medical treatment with DA [50–52]. Normalization of prolactin is achieved in 60–68% of cases, and testosterone levels returned to normal in 40–67% of men with giant prolactinomas [39, 53, 54]. Giant and resistant adenomas may benefit from combining surgical treatment and radiotherapy with DA. Long-term treatment (often lifelong) is required to maintain prolactin suppression and prevent tumor re-growth. A dose decrease is sometimes feasible if long-term normoprolactinemia is maintained together with a decrease in tumor mass size.

Persistent hypogonadism, ranging in different series from 33 to 63% [49], is more common in patients with giant tumors treated with DA, even after normoprolactinemia was obtained. A possible explanation for the lack of testosterone recovery is long-standing invasiveness with irreversible damage to the normal pituitary gonadotroph cells [49].

In summary, prolactinomas in men are usually large and invasive tumors associated with high prolactin levels and hypogonadism. Primary medical treatment is recommended in most cases, with good response to long-term DA treatment, prolactin and testosterone normalization in most cases, along with significant tumor shrinkage and frequently adenoma disappearance. Medical treatment is safe in most men without adverse effects that rarely include mild dizziness, nausea, and behavioral changes.

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Compliance with ethical standards

Conflict of interest The authors have nothing to declare.

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