



# Hyperprolactinemia diagnosis in elderly men: a cohort of 28 patients over 65 years

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## Abstract

**Purpose** To characterize a cohort of elderly men with prolactinomas and their response to treatment.

**Methods** We have identified 28 elderly men diagnosed after the age of 65 with prolactinomas at seven different endocrine clinics in Israel. A retrospective electronic chart review identified a control group of 76 younger men with macroprolactinomas treated in one of the centers.

**Results** Mean age at diagnosis was  $71.3 \pm 5.6$  (range 65–86) years, and current age  $76.6 \pm 7.5$  years. Initial complaints leading to diagnosis included sexual dysfunction in 17 males (61%), headaches in two patients (7%), and visual abnormalities in two (7%). Three men presented with osteoporosis. Ten patients (36%) were diagnosed incidentally following brain imaging for unrelated reasons. Seventeen patients (61%) had macroadenoma, while eleven (39%) presented with a microadenoma or no visible adenoma. Mean prolactin (PRL) at presentation was 1594 (median 382; range 50–18,329) ng/ml. Testosterone was low in 21 men. Patients were treated with cabergoline (max dose,  $1.1 \pm 0.5$  mg/week), except for one given bromocriptine; none required pituitary surgery or radiotherapy. Treatment normalized PRL in 24 patients, and in three men PRL suppressed to  $<2$  ULN. Fifteen men normalized testosterone, three improved without normalization, and in three the normal baseline level increased. After a mean follow-up of 5.3 years, 14/15 patients harboring a macroadenoma showed significant adenoma shrinkage. Most patients reported improvement of low libido/erectile dysfunction. In the control group 60 men (79%) achieved PRL normalization.

**Conclusions** Elderly men with prolactinomas are diagnosed incidentally in 36% of cases. Long-term medical therapy is successful, achieving biochemical remission, adenoma shrinkage, and clinical improvement in almost all patients.

**Keywords** Cabergoline · Elderly · Men · Prolactinoma

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## Introduction

Prolactinoma, the most common functional pituitary adenoma, is usually diagnosed in males as a macroadenoma (diameter  $>10$  mm) [1, 2]. Symptoms of prolactinoma are related to hyperprolactinemia and tumor-mass effect on surrounding tissues. In men, the most common symptom is hypogonadism, with decreased libido, erectile dysfunction, and weakness; followed by headaches or visual field defects, which are related to the enlarged pituitary mass pressing against the optic chiasma [3]. The insidious nature of prolactinoma-associated symptoms and signs in men may induce a delay in the diagnosis of these tumors for extended periods. The main goals in the treatment of patients with prolactinomas are prolactin (PRL) suppression to normal, along with testosterone normalization, tumor size reduction,

and visual improvement [4]. Medical therapy with dopamine agonists (bromocriptine and cabergoline) is considered the first-line treatment in men and women diagnosed with prolactinomas [2–4]. Dopamine agonists' treatment of prolactinomas in men is usually efficient, normalizing PRL in 80–90% and testosterone in 60% of men, inducing tumor shrinkage in >80% while preserving residual pituitary function [4, 5]. Sexual dysfunction is improved in most subjects upon PRL and testosterone normalization [6].

This study reports the clinical presentation and response to treatment of a cohort of 28 elderly male patients with hyperprolactinemia/prolactinoma, who were diagnosed after the age of 65 years.

## Patients and methods

### Patients

The study group consisted of 28 male patients with prolactinomas, who presented at four different academic medical centers and three community-based endocrine clinics in Israel. All men were diagnosed after the age of 65 years. Patients were identified by chart review. Their medical records were reviewed for clinical characteristics, signs and symptoms, laboratory tests, treatment approach, and response to treatment. Tumor size and extension beyond the pituitary sella at presentation and during follow-up were assessed by magnetic-resonance imaging (MRI). A group of 76 younger males (mean age at diagnosis,  $42.8 \pm 12.1$  years) with macroprolactinomas treated at the same time at the Institute of Endocrinology, Rabin Medical Center and identified by electronic database search, served as a control group. The study was approved by the local Institutional Review Board.

Patients were treated by experienced endocrinologists specializing in the field of pituitary diseases. All patients were treated with cabergoline, except for one who was given bromocriptine. The starting oral dose of cabergoline was 0.5 mg, administered once weekly. Doses were increased progressively every 2–4 months, as necessary according to the degree of PRL response, until levels either normalized or plateaued. Serum total testosterone levels were measured in parallel with PRL. Control of PRL secretion was defined as PRL normalization. Patients were considered partially controlled when follow-up PRL levels did not normalize, but were reduced to less than 2-fold the upper limit of normal (ULN).

### Hormonal assays

Hormonal assessment was performed at diagnosis, before medical treatment, and during follow-up. Plasma PRL

levels were measured in the local or reference laboratory of each participating center. In most laboratories, PRL was measured by the commercially available immunometric assay (Immulite 2000, Siemens), which has a sensitivity of 0.15 ng/ml. The intra-assay CVs for PRL concentrations of 22 and 164 ng/ml were 2.3% and 3.8%, respectively; the corresponding inter-assay CV was 6%. Reference levels for men are 5–17 ng/ml. Total testosterone, TSH, FT4, GH, IGF-1, and cortisol were determined by a variety of commercially available immunoassays, according to the site of follow-up treatment. For each patient, all hormonal measurements were performed in the same laboratory.

### Statistical analysis

Categorical variables are presented as numbers and percentages; continuous variables as means and standard deviations, or medians with ranges.

## Results

### Patients' characteristics at presentation

The study cohort included 28 men with PRL-secreting adenomas identified and followed between 2004 and 2018 at seven endocrine clinics in Israel. Mean age at diagnosis was  $71.3 \pm 5.6$  (range 65–86) years, and age at the end of follow-up was  $76.6 \pm 7.5$  (range 66–94) years (Table 1). Mean body mass index (BMI) at presentation was  $28.5 \pm 3.3$  kg/m<sup>2</sup>. Initial complaints leading to diagnosis included sexual dysfunction in 17 (61%), headaches in two (7%), and visual abnormalities in two patients (7%). Three men presented with osteoporosis. One of them had rib fractures. Ten patients were diagnosed incidentally (36%) following brain

**Table 1** Baseline characteristics of 28 elderly male patients with hyperprolactinemia

Parameter	Baseline number
Age at diagnosis $\pm$ standard deviation (years)	$71.3 \pm 5.6$
Current age $\pm$ standard deviation (years)	$76.6 \pm 7.5$
PRL—median, (range) (ng/ml)	382 (50–18,329)
Adenoma type, size (range) (mm)	17 macroa, 7 micro, (4–50)
Hypogonadism— <i>n</i> / <i>N</i> (%)	21/26 (81)
Visual field damage— <i>n</i> (%)	2 (7%)
Hemoglobin $\pm$ standard deviation (g/dl)	$13.5 \pm 1.3$
Sexual dysfunction complaints— <i>n</i> (%)	17 (61%)
Incidental diagnosis— <i>n</i> (%)	10 (36%)

PRL prolactin

**Table 2** Baseline characteristics and response to treatment of patients included in the cohort

No	Age (years)	BMI	Co-morbidity	Size (mm)	Complaints	PRL (ng/ml)	Testosterone	Cab (mg/week)	PRL normalized	Complaint improved	Tumor shrinkage
1	75	25.5	IHD	20	Incidental-syncope	915	Low	0.5	Yes	Yes <sup>a</sup>	Yes
2	71	NA	None	28	Hypogonadism	2135	Low	1.5	Yes	Yes	No
3	69	34.4	IHD	25	Incidental, ED	3799	Low	1	Yes	Yes	Yes
4	66	30.7	IHD	19	Low libido, weakness	573	Low	1	Yes	Yes	Yes
5	83	23	CHF	32	Incidental, head trauma	3213	Low	1.5	Yes	Yes <sup>a</sup>	Yes
6	66	28.7	DM 2	29	Incidental-hearing loss (ED)	3837	Low	1	Yes	NA	Yes
7	68	NA	None	50	Hemianopia, weakness	18,329	Low	1	no F/U	NA	NA
8	68	27.7	IHD	4	ED, libido, headache	112	Normal	1.5	Yes	Yes	NR
9	68	29.8	None	0	ED	294	Low	0.5	Yes	Yes	NR
10	69	27	IFG	17	Incidental-retinal change	>235	Low	0.5	Yes	Yes <sup>a</sup>	Yes
11	67	32.3	DM 2	18	Incidental, headache	1087	Low	1	Yes	Yes <sup>a</sup>	Yes
12	71	31.9	DM 2	Micro	ED	120	Low	BRC	Yes	No	NR
13	69	24.8	DM 2, IHD	9	Incidental-earache (ED)	141	NA	0.5	Yes	Yes <sup>a</sup>	NA
14	69	26.7	DM 2	0	ED	61	Low	0.5	Yes	Yes	NR
15	74	24.6	None	0	Osteoporosis, hypogonadism	358	Normal	1	<2xULN	Yes	NR
16	66	25.4	IFG	11	Hypogonadism	818	Low	2	<2xULN	No	Yes
17	69	28	IHD, CVA	13	Hypogonadism	142	Low	1	Yes	Yes	Yes
18	70	27.5	IHD	20	Hypothyroid, hypogonadism	1935	Undetected	1	Yes	NA	Yes
19	66	28	DM 2, CVA	25	Incidental- stroke	>230	Low	2	Yes	No complaint	Yes
20	78	27.1	None	22	Incidental-dizziness	1970	Normal	2.5	Yes	No complaint	Yes
21	74	29.3	IFG	0	ED, hypogonadism	102	Low	0.5	<2xULN	No	NR
22	81	34	DM 2	12	Osteoporosis	269	Undetected	1	Yes	Yes	NA
23	65	26.5	None	Micro	Osteoporosis	64	Low	0.5	Yes	No complaint	NA
24	67	33.3	DM 2	9	ED, libido, weakness	405	Low	0.5	Yes	Yes	No
25	70	32	IFG	6	ED, weakness, weight gain	50	Low	0.5	Yes	Yes	NA
26	86	31.6	PVD	33	Incidental-fall	415	NA	1.5	Yes	NA	Yes
27	69	28	None	11	ED	55	Normal	0.5	Yes	Yes	Yes
28	82	23.3	IHD	7	Gynecomastia	256	Normal	0.5	Yes	NA	Yes

BMI body mass index, BRC bromocriptine, Cab cabergoline, CVA cerebrovascular disease, DM 2 diabetes mellitus type 2, ED erectile dysfunction, IFG impaired fasting glucose, IHD ischemic heart disease, NA not available, NR not relevant, PRL prolactin, PVD peripheral vascular disease

<sup>a</sup>Libido or weakness improvement, albeit these complaints were not specifically reported before treatment

imaging for unrelated reasons (Tables 1, 2). Seventeen men (61%) had a macroadenoma when diagnosed, while eleven (39%) presented with a microadenoma or no visible adenoma on MRI. Suprasellar extension was evident in 5/17 patients harboring macroadenomas, with two of these presenting with visual field defects. Mean serum PRL level at presentation was 1594 ng/ml (median 382; range 50–18,329). Mean baseline testosterone was  $2.0 \pm 1.1$  ng/ml. Testosterone was low in all but 5 men presenting with normal baseline level, and in two patients in whom testosterone was not recorded at diagnosis. Mean baseline hemoglobin was  $13.5 \pm 1.3$  g/dl (13 men with hemoglobin  $\leq 13$  g/dl). One patient presented with low cortisol level and three had central hypothyroidism; 12/15 of the men who underwent bone mineral density assessment had osteoporosis or osteopenia. The baseline clinical characteristics of the cohort are summarized in Table 1.

The control group consisted of 76 men with macroprolactinomas treated at Rabin Medical Center. All were younger than 65 years when diagnosed (mean age,  $42.8 \pm 12.1$ ; range 17–63 years). Complaints at presentation included sexual dysfunction/decreased libido ( $n = 36$ ), headache ( $n = 24$ ), visual loss (6), neurological symptoms (confusion, vertigo, seizures, parkinson disease, behavioral changes; altogether,  $n = 7$ ), gynecomastia/galactorrhea (5), weakness (3) incidental finding (2), and osteoporosis (1). Mean PRL level at presentation was 7511 ng/ml (range 73–270,000). Baseline testosterone was low in all but 10 men presenting with normal level. Mean adenoma size was 30 mm (range 10–82). Twenty-nine men (38%) had visual field damage. All were treated with dopamine agonists; 15 underwent pituitary surgery.

### Medical treatment for the elderly cohort

Medical treatment with dopamine agonists was provided to all 28 patients following diagnosis. All patients were treated with cabergoline, except for one given bromocriptine; none required pituitary surgery or radiotherapy. Starting dose of cabergoline was usually 0.5 mg/week, and mean maximal dose was  $1.1 \pm 0.5$  (range 0.5–2.5) mg/week. Treatment with dopamine agonists achieved PRL normalization in 24 patients (86%; Tables 2, 3), including the patient on bromocriptine. In three additional men (11%) PRL suppressed to  $<2$  ULN. One patient was lost to follow-up after PRL was suppressed significantly during a short treatment interval. Mean time to PRL normalization in the responding patients was 4.2 (median, 4) months. Fifteen men normalized testosterone, three improved without normalization, and testosterone increased in 3/5 patients with normal baseline level. Two men did not improve their testosterone level including one that did not achieve PRL normalization. Three men with persistent low testosterone during

**Table 3** Response to medical treatment in 28 elderly men with PRL-secreting adenomas/hyperprolactinemia

Response to treatment	Number
PRL normalized ( $n/N$ )	24/27
Testosterone normalized	15
Testosterone improved	6
Macroadenoma shrinkage ( $n/N$ )	12/15
Macroadenoma disappearance ( $n/N$ )	2/15
Complaint improved ( $n/N$ )	17/20 <sup>a</sup>
ED/libido improved ( $n$ )	13

ED erectile dysfunction, PRL prolactin

<sup>a</sup>Three more patients had no complaints at baseline; and five had no follow-up information

dopamine agonist treatment received testosterone replacement. In three men testosterone level was not available following dopamine agonist treatment. Mean hemoglobin level following treatment (13.9 g/dl) did not change. At the end of follow-up, 12/15 patients harboring a macroadenoma with available post-treatment imaging showed significant tumor shrinkage and in two additional subjects the adenoma disappeared (Table 3). Clinically, most of the symptomatic men in the cohort reported disappearance or improvement of their complaints, including 13 patients who had complained of low libido/erectile dysfunction at presentation (Table 3). Several subjects improved weakness and headache.

Currently, after a mean follow-up of 5.3 years, all except one patient continue with dopamine agonist treatment (mean cabergoline dose, 0.7 mg/week), without any significant adverse effects.

### Men diagnosed after the age of 75

Six men of the 28 patients included were at or above 75 (mean age, 80.8 years; range, 75–86) years when diagnosed for the first time (Table 2). All presented incidentally after head imaging for unrelated cause (fall, syncope, head contusion, dizziness) with a macroadenoma (maximal diameter range 12–33 mm), beside one patient with a microadenoma. Mean baseline PRL of these six men was  $1173 \pm 1087$  ng/ml (range 256–3213). Following cabergoline treatment, PRL normalized in all six men and three of them also reported libido improvement, albeit this complaint was not specifically reported when hyperprolactinemia was identified.

### Treatment of the control group

After a mean follow-up treatment of 6.9 years, 60 men (79%) in the younger cohort achieved PRL normalization,

compared to 24 (89%) in the entire elderly cohort and in 15/16 old men (94%) harboring macroadenomas. Nine men (12%) in the young cohort suppressed PRL to  $<2$  ULN, and seven additional subjects (9%) did not achieve PRL control (PRL  $>2$  ULN). Normal testosterone was recorded in 70% of the cohort at the end of follow-up. Of the 42 men with available follow-up imaging data, 34 (81%) showed significant adenoma shrinkage, and vision improved in 16/29 males with visual damage. A statistical comparison between the two groups was not appropriate as the control cohort included only men with macroprolactinomas and not smaller adenomas as the elderly patients, and 15 of the younger men also had pituitary surgery, compared to none in the elderly group.

## Discussion

We report herein a unique group of 28 elderly men with prolactinomas who were diagnosed and treated after the age of 65 years. Men diagnosed with prolactinomas are usually younger, between 30-years and 60-years old [3, 7]. Our study is the first to report medical treatments provided to a population of elderly men with prolactinomas, encompassing ~6–7% of male patients with prolactinomas treated in our clinics. Importantly, in this cohort 17/28 (61%) harbored macroadenomas, 10/28 men (36%) were diagnosed incidentally following brain imaging for unrelated reasons, and almost all males (aside from one lost to follow-up) achieved normal or near-normal PRL levels with dopamine agonist treatment. Most men normalized testosterone levels. However, some of the patients that failed to normalize testosterone could have late-onset hypogonadism associated with advanced age. None required pituitary surgery to achieve hormonal control. Interestingly, patients who were diagnosed incidentally with no specific complaint related to hyperprolactinemia improved clinically following medical treatment, and reported libido and/or weakness improvement. Compared to a cohort of younger men with macroprolactinomas treated in our clinic at the same period, the elderly men responded to treatment with dopamine agonists equally well or even better than their younger counterparts.

Our elderly male patients with prolactinomas diagnosed after the age of 65 years share similar characteristics with females diagnosed with prolactinomas after menopause (mean age at diagnosis, 63–64 years) [8, 9]. Most of these post-menopausal women had macroadenomas, many presented with atypical features for female hyperprolactinemia, including headaches, visual deterioration, or incidental finding of a pituitary mass depicted on CT/MRI [8, 9]; different from younger females diagnosed characteristically with a microadenoma after the appearance of amenorrhea and/or galactorrhea.

There are very few reports in the literature on elderly men with prolactinomas. In a group of 20 men over the age of 75 years randomly selected for dynamic pituitary function tests, one was identified with a large prolactinoma [10]. Delgrange et al. reported nine elderly (aged  $\geq 60$ ; range 60–73 years) men with prolactinomas. Four of these patients came to medical attention for typical features of male prolactinomas (visual field defect, headaches and impotence), whereas the remaining five presented for other reasons including hypopituitarism/cortisol deficiency, vertebral fractures and incidental finding of a pituitary mass [11]. Several other case reports of elderly male patients with prolactinomas included a 71-year-old presenting with memory loss and hydrocephalus [12], a 70-year-old presenting with mild anemia and tiredness [13], and an 80 year-old presenting with recurrent falls, dizzy spells and deteriorating vision [14]. All these patients had macroprolactinomas, and showed that the presentation of a prolactinoma at this advanced age may be heterogeneous and sometimes misleading. However, similar to the response of our patients, dopamine agonists were effective in suppressing PRL in most of the patients, together with resolution of their heterogeneous presenting symptoms [12–14].

Recognition of hyperprolactinemia in elderly patients may be challenging and delayed. Elderly men with prolactinomas are commonly asymptomatic, similar to postmenopausal women [8, 9], as complaints such as decreased libido and erectile dysfunction at an advanced age are usually ignored or not hormonally investigated. Moreover, visual injury from a macroadenoma compressing the optic chiasma may be masked by age-related ophthalmic disorders, including macular degeneration and cataracts. Furthermore, signs like anemia [15], tiredness, hypogonadism and osteoporosis in elderly men may be linked to their advanced age, and delay the diagnosis of hyperprolactinemia in this unique patient population. While, 17 men in our cohort complained of erectile dysfunction and/or low libido, some of them were not concerned but only became cognizant of these symptoms following clinical improvement with medical treatment. This phenomenon was documented by the men with hyperprolactinemia over the age of 75 years. All presented incidentally without the typical features or complaints expected in male prolactinomas, but half reported libido improvement retrospectively, following successful medical treatment with cabergoline.

Patients with prolactinomas treated with dopamine agonists, especially men, may develop impulse control disorders, including hypersexuality, compulsive shopping, financial loss and gambling [16, 17]. Although it is important, our elderly patients were not asked specifically about the possible development of this disorder, and we are not aware that it appeared in men included in the cohort.

## Conclusions

Compared to younger patients, elderly men with prolactinomas may have different clinical characteristics that can delay or prevent their diagnosis. High index of suspicion is required, as these patients usually respond to medical treatment, with rapid clinical improvement.

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## Compliance with ethical standards

**Conflict of interest** Ilan Shimon, has received research grants, consulting, and lectureship fees from Novartis International AG, Medison Pharma, and Pfizer Inc. The remaining authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards.

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