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ORIGINAL ARTICLE

# True hyperprolactinemia in men without visible pituitary adenoma

Ilan Shimon[1,2] · Yaron Rudman[1,2] · Yossi Manisterski[3] · Alex Gorshtein[1,2] · Hiba Masri[1,2] · Hadar Duskin-Bitan[1,2]

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## Abstract

**Purpose** Men with mild to moderate hyperprolactinemia rarely present with normal pituitary on MRI with no visible adenoma, a condition entitled also "idiopathic hyperprolactinemia" or "non-tumoral hyperprolactinemia". We have characterized a cohort of hyperprolactinemic men with normal pituitary imaging.

**Design** We have identified 13 men with true hyperprolactinemia and normal pituitary MRI. Baseline clinical and hormonal characteristics and response to medical treatment were retrospectively retrieved from medical records.

**Results** Mean age at diagnosis was 51 ± 16 years (range, 20–77); mean serum prolactin level at presentation was 91 ng/ml (range, 28–264), eight men presented with low baseline testosterone. Initial complaints leading to diagnosis included sexual dysfunction in ten men and gynecomastia in five. All patients were treated with cabergoline, except for one who was given bromocriptine; none required pituitary surgery. All patients normalized prolactin and testosterone with subsequent clinical improvement reported by most men. Currently, after a mean follow-up of 72 months, ten patients continue treatment with caborgoline (median weekly dose, 0.25 mg), whereas three men discontinued treatment.

**Conclusions** Men with symptomatic hyperprolactinemia may rarely present with normal pituitary imaging. Medical treatment can lead to hormonal improvement with clinical benefit.

**Keywords** Cabergoline · Men · MRI · Prolactinoma

## Introduction

Prolactinomas, benign prolactin (PRL)-secreting tumors, are the most common functional pituitary adenomas, accounting for 60% of secreting pituitary tumors. Prolactinomas are subdivided into microprolactinomas (<10 mm) and macroprolactinomas (≥10 mm) based on their size at presentation [1]. In women most prolactinomas (90%) are microadenomas [2], whereas males present with macroadenomas in 80–85% of the cases, many of them are very large and invasive [3]. Thus, microadenomas account for only 10–15% of all male prolactinomas [4]. Men with mild to moderate hyperprolactinemia may rarely present with normal pituitary MRI imaging and no visible adenoma, and this condition is also entitled "idiopathic hyperprolactinemia" or "non-tumoral hyperprolactinemia". Drug-induced hyperprolactinemia, macroprolctinemia, chronic renal failure and primary hypothyroidism must be excluded, and repeated prolactin measurement 2–3 h after waking up from sleep will establish this rare diagnostic entity of idiopathic hyperprolactinemia. These rare cases will usually imitate very small pituitary microprolactinomas (1–3 mm in diameter) not depicted by the 3-Tesla MRI systems currently in use, similarly to the far more frequent idiopathic hyperprolactinemia commonly encountered in hyperprolactinemic women [5].

Men with idiopathic hyperprolactinemia can present differently from males with micro- or macroprolactinomas, but usually respond to medical treatment with dopamine agonists, with suppression of PRL to normal and subsequent clinical improvement.

As idiopathic hyperprolactinemia is uncommon in men, we report our experience with the diagnosis and treatment of 13 male patients with true hyperprolactinemia and no visible pituitary adenoma on MRI.

✉ Ilan Shimon
ilanshi@clalit.org.il

1 Institute of Endocrinology, Beilinson Hospital, Petach Tikva, Israel

2 Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel

3 Maccabi Health Care Services, Tel Aviv, Israel

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## Patients and methods

### Patients

The study group consisted of 13 male patients with hyperprolactinemia and no visible adenoma on MRI, who presented at three different endocrine clinics in Israel. Their medical records were reviewed for clinical characteristics, signs and symptoms, laboratory tests, treatment approach, and response to treatment. MRI studies (performed once or twice) were also reviewed. This study was specifically approved by the Rabin Medical Center Institutional Review Board (IRB). As this study was retrospective and data collection was anonymous the IRB approval did not require patients' informed consent.

Baseline PRL measurement was repeated at least twice, drug-induced hyperprolactinemia was excluded and macroprolacinemia was eliminated if the clinical scenario was appropriate.

All patients were treated with cabergoline, except for one who was given bromocriptine until recently when switched to cabergoline. The starting oral dose of cabergoline was 0.5 mg, administered once weekly, and adjusted according to hormonal response. Serum total testosterone levels were measured in parallel with PRL. Control of PRL secretion was defined as PRL normalization. The patients were followed every 4–6 months during the first year following diagnosis, and frequency decreased later to once yearly or as required.

### Hormonal assays

Hormonal assessment was performed at diagnosis, before medical treatment, during follow-up, and when applicable following cabergoline discontinuation. Fasting morning PRL was tested 2–3 h after waking up from sleep, and measured in the local or reference laboratory of each participating center. Following the first test of elevated PRL, repeated plasma measurement was performed. 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, LH, FSH, 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.

### Pituitary imaging

All patients included underwent sellar MRI before initiation of dopamine agonist treatment. Pituitary imaging performed before 2014 used a 1.5-Tesla MRI, and afterwards men underwent imaging with a 3-Tesla MRI machine.

### Statistical analysis

Categorical variables are presented as numbers and percentages; continuous variables as means and standard deviations, or medians with ranges. For group comparisons, we used the Student's $t$ test to analyze differences in numerical variables. Observed differences were assumed to be statistically significant if the probability of chance occurrence (two-sided $p$ value) was less than 0.05.

## Results

### Patients' characteristics at presentation

The study cohort included 13 men with hyperprolactinemia identified and followed between 1998 and 2019 at three endocrine clinics in Israel. This reflects ~4% of our cohort of men with real hyperprolactinemia. Mean age at diagnosis was 51 ± 16 (range, 20–77) years (Table 1). Initial complaints leading to diagnosis included sexual dysfunction in ten, and gynecomastia in five patients, one of them had also galactorrhea. Symptoms appeared between 0.5 and 3 years before diagnosis of hyperprolactinemia. Mean serum PRL level at presentation was 91 ng/ml (median, 51; range, 28–264). Seven of the men presented with PRL level ≤3 x upper limit of normal (≤ 51 ng/ml). Mean baseline testosterone was 2.66 ± 0.9 ng/ml (normal, 2.8–9 ng/ml). Testosterone was low in most patients, but 5 men presented with normal baseline level, albeit at the low normal range (Table 2; range, 3–4.3 ng/ml). Baseline LH was between 1.8 and 5 IU/L and FSH between 1.8 and 6.7 IU/L, beside one patient

**Table 1** Baseline characteristics of 13 men with true hyperprolactinemia and normal sellar imaging

| *N* | 13 |
|---|---|
| Age (years) | 51 ± 16 (range, 20–77) |
| Sexual dysfunction, *n* | 10 |
| Gynecomastia, *n* | 5 |
| PRL(ng/ml) | 91 (range, 28–264). |
| Testosterone (ng/ml) | 2.66 ± 0.9 (range, 1.8–4.3) |
| Hypopituitarism | None |
| Mean follow-up (months) | 72 (range, 3–230) |

Data is presents as mean ± SD and/or range, when indicated

**Table 2** Baseline characteristics and response to medical treatment of each patient in the cohort

| No | Age years | PRL ng/ml normal 5–17 | | Testo ng/ml normal 2.8–9 | Complaints | Max CAB dose mg/week | CurrentPRL ng/ml | Current Testo ng/ml | Complaints improved | Current CAB mg/week |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 68 | | 100 | 4.3 | Low libido, ED | 1.5 | 12 | 3.5 | Libido | 1.5 |
| 2 | 68 | | 264 | 1.9 | ED | 0.5 | 7 | 6.9 | Libido | 0.25 |
| 3 | 54 | | 50 | 3.3 | Low libido, ED | 0.5 | 7 | 4.3 | Libido | 0.5 |
| 4 | 34 | | 57 | 1.8 | Gynecomastia; galactorrhea | 0.5 | 7 | 2.9 | No | Discontinue |
| 5 | 45 | | 45 | 2.8 | Gynecomastia | 0.5 | 1 | 4.1 | N/A | 0.5 |
| 6 | 77 | | 38 | 3.0 | ED, low libido, gynecomastia | 0.25 | 6 | 6.6 | Gynecomastia | 0.25 |
| 7 | 67 | | 44 | 2.7 | Gynecomastia; low libido | 0.5 | 13 | 6.3 | Gynecomastia | 0.2 |
| 8 | 20 | | 114 | 3.3 | Gynecomastia | 0.5 | 4.5 | 3.1 | No | Discontinue |
| 9 | 34 | | 224 | 2.7 | ED, low libido | BRC-7.5/d | 8 | 4.4 | Libido/ED | 0.5 |
| 10 | 44 | | 51 | 1.9 | Hypogonadism | 0.5 | 9 | 4.9 | N/A | Discontinue |
| 11 | 54 | | 28 | 3.6 | ED | 0.5 | 19 | 4.8 | Libido/ED | 0.125 |
| 12 | 40 | | 38 | 2.5 | ED, Low libido, weakness | 0.5 | 2 | 4.4 | Libido | 0.25 |
| 13 | 58 | | 130 | 2.6 | Low libido | 0.5 | 7.5 | 5.7 | Libido/ weakness | 0.25 |

*BRC* bromocriptine, *CAB* cabergoline, *ED* erectile dysfunction, *N/A* not available, *PRL* prolactin, *Testo* testosterone

with azoospermia and FSH elevated up to 43 IU/L. Mean baseline hemoglobin was 14.3 ± 0.7 gr/dl. All patients in the cohort had intact pituitary function. IGF-1 was measured in ten patients and was within the normal range. Thyroid function tests were normal in all patients, including one man replaced for hypothyroidism.

MRI on presentation demonstrated normal pituitary in all patients. Two men underwent repeated imaging with similar results.

The baseline clinical characteristics of the men included in the cohort are summarized in Table 1.

## Medical treatment

Medical treatment with dopamine agonists was given to all affected men following diagnosis. All patients were treated with cabergoline, except for one who was given bromocriptine (starting dose of 7.5 mg/day, gradually decreased to 1.25 mg/day) until recently when switched to cabergoline; none required pituitary surgery. Starting dose of cabergoline was usually 0.5 mg/week, and mean maximal dose was 0.58 (range, 0.5–1.5) mg/week. Treatment with dopamine agonists achieved PRL normalization in all patients (Table 2), including the patient on bromocriptine. Mean baseline PRL decreased from 91 ± 72 to 7.9 ± 4.5 ng/ml ($p < 0.005$). Time to PRL normalization ranged between 1 and 4 months. Mean testosterone increased from a baseline of 2.66 + 0.9 to 4.8 ± 1.2 ng/ml ($p < 0.001$). All men with low baseline concentrations normalized testosterone upon PRL suppression. Testosterone increased significantly in 3/5 patients with low normal baseline level (Table 2). Currently, after a mean follow-up of 72 months, ten patients continue with dopamine agonist treatment (median current cabergoline dose, 0.25 mg/week), and three patients discontinued treatment. Clinically, seven patients reported improvement of their sexual dysfunction/low libido complaints following medical treatment, and two men experienced gynecomastia retreat (Table 2). Two patients did not improve clinically, including the man with elevated FSH (Table 2, patient 4), and relevant clinical information is not available for two other men. Three out of five men discontinuing treatment (including two other patients that resumed cabergoline later) experienced PRL increase following cabergoline discontinuation. The three patients that discontinued treatment did not report any clinical improvement (testosterone increased in two). Men that continue with dopamine agonists experienced good clinical response. Mean hemoglobin level following treatment (14.6 gr/dl) was not different from the baseline level. Four men underwent bone mineral density assessment that demonstrated lumbar spine osteopenia in two, femoral neck osteopenia in one and osteoporosis in one. The man with

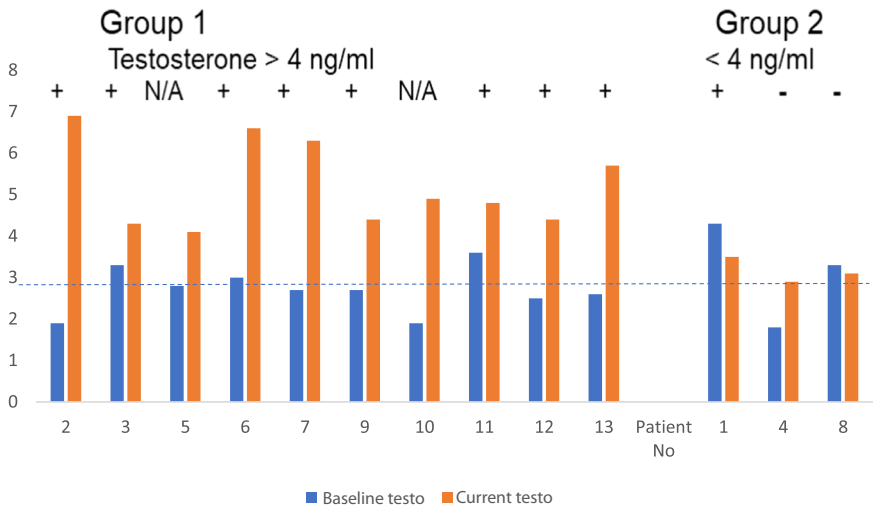


**Fig. 1** Baseline and current testosterone (ng/ml; normal, 2.8–9; lower normal limit highlighted by the dashed line) following medical treatment, and clinical response. + clinical response, − no clinical response, N/A clinical information is not available

osteoporosis improved following bisphosphonate treatment. Two patients with osteopenia and follow-up examination improved bone density following cabergoline treatment.

### Clinical impact of testosterone elevation

The patients were classified according to testosterone rise following treatment with a dopamine agonist. Ten patients (group 1) achieved testosterone >4 ng/ml (Fig. 1, mean testosterone following treatment, 5.2 ± 1.0 ng/ml; normal, 2.8–9 ng/ml). Three men (group 2) showed post-treatment testosterone <4 ng/ml (Fig. 1, mean, 3.2 ng/ml). Remarkably, all eight men with available data included in group 1 improved clinically, compared to only one man in group 2.

## Discussion

Men with hyperprolactinemia usually harbor macroprolactinomas, and microadenomas are infrequent. Male hyperprolactinemia without a visible pituitary adenoma is rare compared to the high incidence in females [5, 6]. These men usually have mild disease with lower PRL levels and milder symptoms. Patients may be incidentally discovered, but usually symptoms related to hypogonadism (libido loss, erectile dysfunction, gynecomastia) will lead to the diagnosis of hyperprolactinemia. Mass effect signs including chiasmal compression or headache characteristically seen in men with macroadenomas are obviously not encountered in patients with non-tumoral hyperprolactinemia.

Hyperprolactinemia with no visible tumor may result from very small microprolactinomas not depicted by MRI. It can be also associated with enlarged sella (secondary partial empty sella) following suspected prolactinoma apoplexy [7], or a rare case of idiopathic lactotroph hyperplasia [8]. With the improvement of pituitary MRI imaging techniques entered in the last two decades, fewer cases of non-tumoral hypeprolactinemia are diagnosed in females and males, as extremely small microprolactinomas of 2–3 mm may be depicted by such advanced technologies. Noteworthy, only five men included in this cohort performed their pituitary MRI earlier than 2010, whereas all others had advanced MRI studies performed during the last years. Notably, among 14 women with hyperprolactinemia and normal pituitary imaging studies followed for years, four developed finally radiographic evidence of a small pituitary microadenoma [9]. This may reflect the improved pituitary imaging occurred during the years of follow-up or the natural size increase of tiny microadenomas.

Only few patients in our series were tested for macroprolactin that was negative, and all others were treated with cabergoline following a repeated test that confirmed the presence of hyperprolactinemia as a possible reason for their complaints. The prevalence of macroprolactinemia is ~20% in hyperprolactinemic patients [10] with reproductive manifestations. Almost all patients with true hyperprolactinemia are symptomatic compared to patients with macroprolactinemia that present with lower rate of symptoms associated with hyperprolactinemia [11]. As all our patients had symptoms compatible with true hyperprolactinemia with low or marginally low testosterone levels, and treatment with dopamine agonists suppressed PRL to normal with simultaneous testosterone elevation and symptomatic improvement in most men, we assume that these men had true non-tumoral hyperprolactinemia and not macroprolactinemia. Thus, symptomatic patients with hyperprolactinemia and negative sellar imaging should receive dopamine agonist treatment, while for

asymptomatic individuals macroprolactinemia should be screened and excluded, before medical therapy is considered [12]. Noteworthy, in our cohort, men with better testosterone response to cabergoline treatment (Fig. 1, group 1) had improved clinical response, emphasizing the importance of dopamine agonist treatment in hyperprolactinemic patients with hypogonadism.

Prolactinomas in women and men respond to cabergoline, achieving PRL normalization in 85–95% of microprolactinomas, and 75–85% for macroprolactinomas [4, 13, 14]. In our cohort, all patients responded to cabergoline with PRL suppression to normal. This is in line with the trend of small prolactinomas to respond better to dopamine agonist treatment compared to macroadenomas or giant prolactinomas in men [15]. Moreover, the cabergoline dosage used was relatively low, and patients were continuously maintained and controlled with a median dose of 0.25 mg/week. However, men that discontinued dopamine agonist treatment experienced relapse of hyperprolactinemia.

In conclusion, men with symptoms of hypogonadism rarely present with hyperprolactinemia without visible pituitary adenoma. This true hyperprolactinemia, albeit mild, responds to treatment with dopamine agonists together with subsequent clinical improvement in most men, thus highlights the benefit patients with such a rare condition may obtain.

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## Compliance with ethical standards

**Conflict of interest** The 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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