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Male prolactinomas presenting with normal testosterone levels

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Abstract In men harboring prolactinoma the most common symptoms are related to hypogonadism, including decreased libido, erectile dysfunction, and gynecomastia. These men characteristically present with elevated serum prolactin (PRL) levels, suppressed gonadotropins, and low testosterone levels. We studied a group of 11 unique men with prolactinomas presenting with testosterone levels within the normal range (≥2.6 ng/ml; cohort A), and compared them to 11 prolactinoma men with borderline baseline testosterone (2.1–2.5 ng/ml; cohort B) and to a cohort of 34 prolactinoma patients with low testosterone levels (≤2 ng/ml; cohort C). Mean testosterone levels at presentation were 3.91 ± 0.9 ng/ml in cohort A (range, 2.6–5.2 ng/ml), 2.44 ± 0.16 ng/ml in cohort B and 0.96 ± 0.6 in cohort C ($p < 0.001$). Mean baseline PRL levels were >20 times above normal in cohort A compared to >100 times above normal in cohorts B and C. Symptoms of hypogonadism were present in 55, 64 and 76 % of men in groups A, B and C, respectively. There was a trend towards a larger tumor size in the low testosterone group ($p = 0.06$). Visual fields defects at presentation were more prevalent in this cohort (C). With cabergoline, testosterone level increased from 3.91 to 6.42 ng/ml ($\Delta = 2.51$ ng/ml) in cohort A, from 2.44 to 5.63 ng/ml ($\Delta = 3.19$ ng/ml) in cohort B, and from 0.96 to 3.30 ng/ml ($\Delta = 2.34$ ng/ml) in cohort C ($p < 0.05$ for each group). Symptoms of hypogonadism improved following treatment in 83 % of symptomatic men in cohort A. Normal testosterone does not exclude the likelihood of prolactinoma in men. When treated with cabergoline, testosterone levels in these men can increase higher within the normal range together with clinical improvement.

Keywords Cabergoline · Hypogonadism · Men · Prolactinoma · Testosterone

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Introduction

Prolactinomas are benign hormone-secreting pituitary tumors, account for a third of all pituitary adenomas and occur both in women and men. In men, usually harboring macroadenomas, the most common symptoms are related to hypogonadism, including decreased libido, erectile dysfunction, and gynecomastia [1]. Men usually present with elevated serum prolactin (PRL) levels, suppressed gonadotropins, low testosterone levels [2] and mild anemia [3]. Medical therapy with dopamine agonists (bromocriptine and cabergoline) is considered to be the first-line treatment for both men and women with prolactinomas [4–6]. Dopamine agonist treatment for men with prolactinomas has shown significant efficacy in suppressing and normalizing PRL levels in most affected male patients, inducing tumor shrinkage, improving sexual function and other complaints, and normalizing testosterone levels in most cases [7, 8].

Traditionally, the insidious nature of prolactinomas-associated symptoms and signs in men results in a delay in the diagnosis of these tumors; even men with very high PRL and low testosterone levels may be diagnosed after several years of nonspecific complaints [1]. Headaches or visual deterioration related to the enlarged pituitary mass may call for an early diagnosis [9]. Low serum testosterone and complaints linked to hypogonadism, or unexplained

anemia and decreased bone mass [10] may serve as other clues and indication to ask for PRL measurement, required for prolactinoma diagnosis in men.

We report here a series of unique male patients with prolactinomas that presented with testosterone levels within the normal range, although having very high PRL levels when diagnosed. The study compares these patients to the more typical prolactinoma patients presenting with low serum testosterone levels, and also to a cohort of men with borderline levels of testosterone, in order to define clinical and hormonal characteristics and prognostic factors of severity and cure in these three patient cohorts with low or normal testosterone levels.

Patients and methods

The study population included 56 men with prolactinomas that were classified to 3 cohorts according to their baseline testosterone levels as follow: 11 men (Cohort A) that presented with normal testosterone levels (≥2.6 ng/ml), 11 patients (Cohort B) presenting with marginal testosterone levels (2.1–2.5 ng/ml), and 34 consecutive subjects (group C) with significantly low testosterone levels (≤2 ng/ml) when diagnosed. All were diagnosed, treated and followed in the Endocrine Clinic at Beilinson Hospital, Petah-Tiqva, Israel. Information on clinical presentation, laboratory tests [total testosterone level, PRL, cortisol, thyroid function tests, LH, FSH, GH and IGF-1; biochemistry; complete blood counts (CBC)], pituitary imaging and visual field assessment, at presentation and during follow-up period were collected. Response to cabergoline treatment and clinical improvement were also reviewed. The study was approved and conducted according to the local ethical institutional review board.

Cabergoline treatment protocol

All patients including the men presenting with normal testosterone levels were treated with the dopamine agonist cabergoline. The starting oral dose of cabergoline was 0.5 mg, administered once weekly from the first week. Doses were increased progressively every 2 months, as necessary, according to the degree of PRL suppression, until levels normalized. Serum total testosterone level was measured in parallel with PRL. Sellar MRI was performed before treatment, 6 months after onset of treatment, and then as required according to the patient clinical response.

Biochemical evaluation

Serum morning PRL levels were measured twice on 2 different occasions by immunometric assay (Immulite 2,000; Siemens), which has a sensitivity of 0.15 ng/ml. The intra-assay coefficients of variation (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 in our laboratory are 5–17 ng/ml. Levels higher than 200 ng/ml were calculated after appropriate serum dilutions. Morning total testosterone measured also at least twice at presentation before treatment was determined by radioimmunoassay (Coat-A-Count) which has a sensitivity of 0.1 ng/ml; the intra- and inter-assay CVs were 4 and 10 %, respectively. Reference levels for total testosterone ranged from 2.6–10 ng/ml in men. CBCs were measured using an automatic ABX Micros CRP 200 analyzer (Clinical Laboratory International, Brussels, Belgium).

Statistical analysis

Statistical calculations were performed with the SigmaStat 2.03 (Systat Software Inc., Point Richmond, CA, USA) computerized program. Results are expressed as mean ± standard deviation unless otherwise indicated. For comparison between groups the independent Student's *t* test or one-way analysis of variance were done in order to analyze differences between numerical variables, and Chi Square test or Fisher Exact Test were used for differences between categorical variables. The paired Student's *t* test was used to analyze variables before and after intervention. The Pearson product was used for analysis of correlations between variables. Observed differences were assumed to be statistically significant if the probability of chance occurrence (p value) was <0.05.

Results

The clinical characteristic of the study group are shown in Table 1. Symptoms of hypogonadism were reported by 2/3 of the whole group, while 25 % of the patients had visual defects or other hormonal axis involvement. The study group was divided to 3 cohorts according to baseline testosterone: normal (A, n = 11), marginal low (B, n = 11), low (C, n = 34) and the clinical characteristics of each group are shown in Table 2. The mean age and maximal tumor diameter were similar between groups, with a trend towards a bigger size in the low testosterone group (Table 2). Pituitary tumors ≤10 mm were found in 27, 18 and 18 % of men in cohorts A, B and C, respectively. All patients (beside one in cohort C) had visible adenoma. Mean testosterone levels at presentation were 3.91 ± 0.9 ng/ml in cohort A (range, 2.6–5.2 ng/ml; 5 patients had testosterone levels ≥4 ng/ml), 2.44 ± 0.16 ng/ml in cohort B and 0.96 ± 0.6 in cohort C ($p < 0.001$). Mean baseline PRL levels were >20 times above normal in the normal testosterone group (mean,

Table 1 Baseline clinical characteristics of all prolactinoma patients included in the study

n	56
Age (years) ± SD	48.4 ± 13.5
Size of tumor (mm)	21.8 ± 12.3
Suprasellar extension	37 %
Prolactin (ng/ml)	1,847 ± 2,947
Testosterone (ng/ml)	1.83 ± 1.3
LH (mIU/ml)	1.57 ± 1.2
FSH (mIU/ml)	2.76 ± 2.9
One or more affected pituitary hormones	22 %
Visual defect	25 %
Sexual dysfunction	69 %

559 ± 370 ng/ml; 10/11 with PRL >100 ng/ml, 9/11 had PRL >200 ng/ml, 6/11 of men had PRL >500 ng/ml), compared to >100 times above normal in the marginal (8/11 subjects had PRL >100 ng/ml) and low testosterone groups (31/34 subjects with PRL >100 ng/ml) (Table 2). PRL was marginally significantly higher in Cohort C compared to Cohort A.

Symptoms of hypogonadism (erectile dysfunction, decreased libido, gynecomastia) were present in 55, 64 and 76 % of men in groups A, B and C, respectively. Visual fields defects at presentation were more prevalent in the low testosterone group (37 %; $p = 0.07$), whereas the mean hemoglobin level was slightly low in all groups. One or more pituitary axes (not including testosterone) were affected in 9, 18 and 28 % of patients in groups A, B and C, respectively (Table 2; NS).

Prolactinoma treatment

Medical treatment with cabergoline was the treatment of choice in all patients in the three groups. One patient in group B and six patients in group C underwent also transsphenoidal pituitary adenoma resection. The mean weekly cabergoline dose was similar in all cohorts, 1.1 mg (range, 0.5–5 mg/week). Cabergoline normalized PRL in 89 % of patients in group A, 80 % in group B and 88 % in group C. Testosterone level increased significantly from 3.91 ± 0.9 to 6.42 ± 1.9 ng/ml ($\Delta = 2.51$ ng/ml) in cohort A, from 2.44 ± 0.16 to 5.63 ± 1.77 ng/ml ($\Delta = 3.19$ ng/ml) in cohort B, and from 0.96 ± 0.6 to 3.30 ± 1.5 ng/ml ($\Delta = 2.34$ ng/ml) in cohort C ($p < 0.05$ for each group, NS in between groups) (Figs. 1, 2). Normalization of testosterone was achieved in 90 % at group B and 74 % at group C (p = NS). Data is missing for 2 patients in cohort A, one in cohort B, and 3 in cohort C. The number of patients that failed to increase significantly testosterone levels (Δ >1 ng/ml above baseline testosterone) after PRL suppression, was similar between groups (22, 10 and 19 % n groups A, B and C, respectively). There was no correlation between PRL and testosterone levels at diagnosis in any of the three patient groups. There was a negative correlation between baseline PRL and testosterone increase after cabergoline treatment in cohort C ($p = 0.055$). Hemoglobin level increased significantly from 13.3 to 14 gr % in cohort A, from 13.5 to 13.9 gr % in cohort B, and from 13.7 to 14.4 gr % in cohort C ($p < 0.05$ for all group) following PRL suppression. Symptoms of hypogonadism improved following PRL normalization and testosterone increase, in 83 % of the symptomatic patients with normal baseline testosterone (Cohort A). The only man in cohort A that did not improve clinically is the one that did not suppress PRL to normal while his testosterone did not increase. All the others with clinical benefit suppressed PRL to normal together with testosterone increase within the normal range. Tumor shrinkage was noticed in most patients who had sellar imaging following medical treatment. In cohort A, 7 out of 9 prolactinomas decreased significantly in size following cabergoline treatment.

Table 2 Baseline clinical characteristics of prolactinoma patients included in the three cohorts

Cohort	A: Normal testosterone, ≥2.6 ng/ml	B: Marginal low testosterone, 2.1–2.5 ng/ml	C: Low testosterone, ≤2.0 ng/ml	*p*
n	11	11	34	
Age (years) ± SD	45.6 ± 13.7	51.9 ± 11.9	48.2 ± 14	NS
Size of tumor (mm)	15.9 ± 9.1*	21.6 ± 13.2	23.9 ± 12.5*	NS
Suprasellar extension	11 %*	25 %	48 %*	0.1
Prolactin (ng/ml)	559 ± 370*	2,052 ± 1,977	2197 ± 3543*	NS
Total testosterone (ng/ml)	3.91 ± 0.9	2.44 ± 0.16	0.96 ± 0.6	<0.001
LH (mIU/ml)	1.86 ± 0.7	2.23 ± 0.9	1.34 ± 1.3	NS
FSH (mIU/ml)	3.39 ± 3.7	4.06 ± 2.6	2.15 ± 2.6	0.03
One or more affected pituitary hormone	9 %	18 %	28 %	NS
Visual defect	9 %	9 %	37 %	0.07
Sexual dysfunction	55 %	64 %	76 %	NS

* $p = 0.06$; between groups A and C

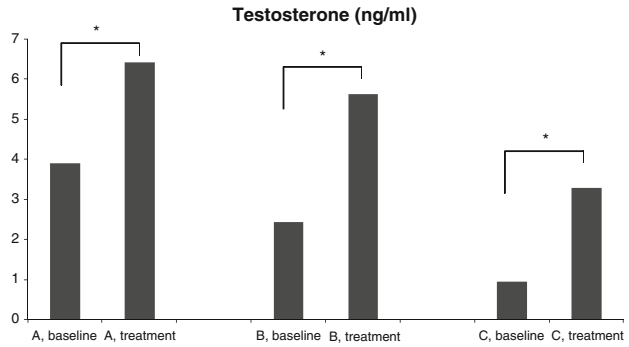

Fig. 1 Mean testosterone levels in prolactinoma patients before and after treatment with cabergoline according to baseline testosterone levels. Normal testosterone ≥2.6 ng/ml. Normal baseline testosterone (Cohort *A*); marginal low (*B*); and low (*C*). *$p < 0.05$; for each group

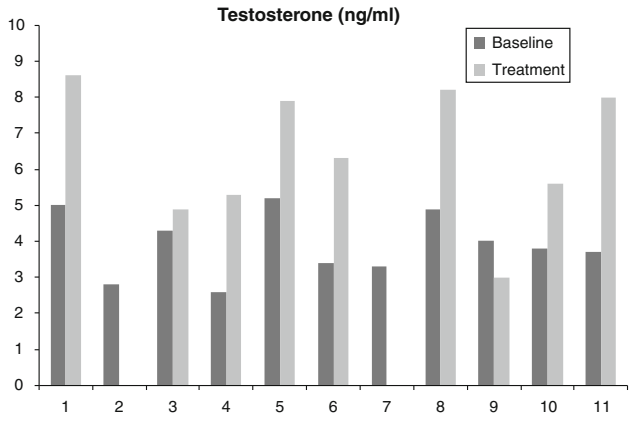

Fig. 2 Testosterone levels in 11 prolactinoma patients with normal baseline testosterone before (*dark grey*) and following (*light grey*) treatment with cabergoline. Post-treatment data is missing for patients 2 and 7. Normal testosterone ≥2.6 ng/ml

Discussion

The classical hallmark of prolactinomas in males beside elevated PRL level, is a suppressed serum testosterone accompanied by symptoms of hypogonadism. Our study demonstrates that about 40 % of men with prolactinomas in our cohort presented with normal or borderline testosterone levels. However, when these men were treated with a dopamine agonist and PRL was suppressed to normal, testosterone levels increased further to higher concentrations within the normal range. Interestingly, the extent of testosterone increase was similar in subjects with low, borderline and normal baseline testosterone, albeit the final testosterone level was higher in patients that presented with higher (normal or borderline) testosterone. Moreover, the proportion of patients complaining of symptoms related to hypogonadism was similar in the three cohorts, and almost all men presenting with normal testosterone and sexual dysfunction improved clinically when their testosterone was raised further following cabergoline treatment. This emphasizes that the assumed normal testosterone in cohort A at presentation is in fact lower than the "true" testosterone for these men, which was achieved only when PRL was medically suppressed. Only then symptoms of hypogonadism improved.

Why do patients in cohort A have higher or normal testosterone levels when diagnosed? Patients in this group presented with smaller and less invasive tumors, and with lower PRL levels compared to patients in cohort C. While these tumors are less aggressive, and have no damage on the gonadotroph cell population as the more invasive tumors in cohort C are, patients harboring these adenomas may retain an intact pituitary–gonadal hormonal axis, stimulating more testosterone production, both before treatment initiation and while on cabergoline. Men with the more aggressive tumors suffering from permanently damaged gonadotrophs due to tumor mass pressure, in addition to the hyperprolactinemia-induced testosterone suppression, present with lower testosterone levels that increase after PRL normalization, but still to lower levels, compared to patients with higher baseline testosterone concentrations. This is revealed by the negative association between baseline PRL and testosterone increment in men included in group C.

This phenomenon of prolactinomas in men accompanied by normal testosterone levels has been reported, but there is limited data regarding its true prevalence among affected subjects. Moreover, previous studies did not characterize these men, compared to men harboring the more typical prolactinomas. Also, the concept that testosterone improvement within the normal range may be associated with symptomatic improvement is important and new. In a series of 28 men with prolactinomas reported by Ono M et al. [11] 12 men had normal pretreatment testosterone (mean of 4 ng/m) that increased in 10 of these patients after PRL normalization (to a mean of 5.4 ng/ml). Iglesias et al. [12] reported a series of 88 men with prolactinomas, 26 % of the patients with macroprolactinomas had testosterone >3.5 ng/ml. Sibal et al. [13] have summarized the records of 35 men with macroprolactinomas, and identified 8 men (23 %) with unaffected gonadotropin-testosterone axis. Thus, these series with male prolactinomas contain between 23 and 42 % subjects presenting with normal or near-normal pre-treatment testosterone, similarly to our cohort.

Most of the patients in our cohort had baseline PRL levels >100 ng/ml (91 % of the patients presenting with normal testosterone), and 55/56 had visible pituitary tumor on MRI, most were macroadenomas. We did not assess the presence of macroprolactin in our patients, but it is clear that our cohort included subjects harboring PRL-secreting adenomas with true hyperprolactinemia. Interestingly,

macroprolactinemia can be detected in some patients with prolactinomas [14], and in 27 % of macroprolactinemic patients a pituitary adenoma can be depicted [15]. Moreover, some patients with macroprolactinemia displayed typical hyperprolactinemia-associated clinical symptoms, and treatment with dopamine agonist achieved clinical improvement [14].

We conclude that men complaining of sexual dysfunction with normal or borderline testosterone measurements may still harbor a prolactinoma and PRL measurement should not be missed. Moreover, as restoring gonadal function is an important endpoint of hyperprolactinemia treatment, one should bear in mind that sexual dysfunction in men with normal testosterone is a common scenario and should not exclude the diagnosis of prolactinoma, ensuring that optimal treatment to normalize PRL will improve their symptoms.

Conflict of interest The authors declare that they have no conflict of interest.

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