Predicting hypogonadotropic hypogonadism persistence in male macroprolactinoma

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Abstract

Purpose To study the baseline characteristics predicting hypogonadotropic hypogonadism (HH) persistence in men with macroprolactinoma that achieved prolactin normalization.

Design Retrospective cohort study.

Methods Male patients diagnosed with macroprolactinoma and HH that received cabergoline treatment with subsequent prolactin normalization were included: men that achieved eugonadism, and men that remained hypogonadal. Patient’s demographic, clinical and biochemical parameters, sellar imaging, and visual fields tests were obtained. Univariate and multivariate models were used to identify predictors of HH persistence.

Results Fifty-eight male patients (age 49.2 ± 12.6 years) with a median baseline prolactin of 1154 ng/mL (IQR 478–2763 ng/mL) and adenoma (maximal) diameter of 25.9 ± 14.8 mm were followed for a median of 5.6 years (IQR 3.0–10.7). Twelve men (21%) suffered from HH persistence at the end of follow-up and 46 men achieved eugonadism. Forty-two out of 46 men (91%) accomplished eugonadism within the first year following prolactin normalization. In a multivariate logistic regression model, hypopituitarism (OR 10.1; 95% CI 1.10–101.94), visual field defect (OR 9.9; 95% CI 1.07–92.33), and low baseline testosterone levels (OR 0.5; 95% CI 0.29–0.93) were independent predictors of HH persistence.

Conclusion In our cohort of men with macroprolactinoma that reached prolactin normalization with cabergoline treatment, 21% had HH persistence. Pituitary hormone deficiency, visual field defects, and low baseline testosterone levels were independently associated with HH persistence. 91% of men achieved eugonadism within the first year following prolactin normalization. These findings may support informed clinical decision-making regarding the initiation of testosterone replacement in men with macroprolactinomas.

Keywords Men · Prolactinoma · Prolactin · Testosterone · Hypogonadism

Introduction

Prolactinomas (i.e., prolactin-secreting adenomas) are the most common functional pituitary tumors, accounting for 40–60 percent of all pituitary tumors [1, 2]. Prolactinomas larger than 10 mm in diameter (i.e., macroprolactinomas) exhibit male predominance and a tendency to a more aggressive course, as compared with smaller prolactinomas [3, 4].

Symptoms secondary to mass effect are encountered in 29–54% of men [5–7]. These symptoms develop as the tumor presses against critical sellar and parasellar structures, leading to visual field defects (VFD), headaches, and rarely ophthalmoplegia. Patients may suffer from central hypothyroidism (present in 18–41% of affected men) and central adrenal insufficiency (12–67% of men) [5, 8, 9].

Men with macroprolactinomas frequently present with symptoms secondary to hyperprolactinemia. Hypogonadotropic hypogonadism (HH) occurs in approximately 76–100% of men at the time of diagnosis [10, 11], clinically reflected by erectile dysfunction, decreased libido, and decreased sperm counts. Low serum testosterone levels may cause secondary anemia in up to 83% of men [12].

Previous studies suggest that HH in patients with macroprolactinoma derives primarily from the inhibitory effect of
prolactin on the hypothalamus [13], with incidental cases of HH resulting from direct structural pituitary damage caused by large tumors [14].

Medical treatment with cabergoline is recommended as first-line therapy for patients with symptomatic prolactinomas [15]. The main goals of treatment for men include prolactin normalization, tumor mass reduction and gonadal axis recovery [16].

With cabergoline treatment, HH persistence is seen in 11–73% of men with macroprolactinoma [7–11, 17, 18]. Because of the small sample size in the different studies, the variable tumor size, the changing duration of treatment and follow-up, and the diverse ethnicity of the populations studied, there is a considerable between-studies variability in the proportion of men with HH persistence. Moreover, some studies included patients with dopamine agonist resistance or with normal baseline testosterone levels, while others included patients that underwent surgery and radiation (treatments that may result in HH persistence), which may have caused incorrect patient classification.

De Rosa et al. (Italy) [10] prospectively evaluated 38 medically treated male patients with macroprolactinoma and identified high baseline serum prolactin, low baseline testosterone and large tumor size as predictors of short-term HH persistence (up to 6 months after prolactin normalization). In 2020, Sehemby et al. [11] investigated a cohort of 30 men from Mumbai, India, that achieved normoprolactinemia with cabergoline therapy. They found that baseline serum prolactin and tumor size predicted HH persistence after a median follow-up of 2 years (after prolactin normalization).

This study aims to identify the baseline characteristics predicting long-term HH persistence in a cohort of men with macroprolactinoma, who achieved normoprolactinemia following medical treatment with cabergoline. This study also reports the long-term response to medical treatment in this population, with and without HH persistence.

Study design and methods

This is a single-center retrospective study of male macroprolactinoma, treated at the pituitary clinic at the Institute of Endocrinology, Beilinson Hospital, Rabin Medical Center (RMC), Israel. The study was approved by the institutional ethics review board.

Patients

Patients were identified by reviewing the pituitary clinic prolactinoma registry at RMC. All patients were diagnosed or referred directly after prolactinoma detection to the pituitary clinic at the RMC. Male patients with pituitary macroadenoma (over 10 mm in maximal diameter) on magnetic resonance imaging (MRI) and hyperprolactinemia were included.

Based on the criteria published by Karavitaki et al. [19], patients with baseline prolactin levels below 100 ng/mL were not included, in order to exclude men with hyperprolactinemia secondary to antipsychotic medication use or “pituitary stalk effect”.

All included patients were treated with cabergoline monotherapy and achieved prolactin normalization.

We excluded men that did not reach normoprolactinemia (i.e., dopamine agonist resistant patients), men with eugonadism at presentation, and men with less than 12 months of follow-up. Men that underwent surgery or radiotherapy were also excluded, as these treatments may induce gonadotropin deficiency.

Data collection

Patient’s demographic, clinical and biochemical parameters, sellar MRI and visual fields tests (interpreted by a neuro-ophthalmologist) were obtained. Laboratory tests at presentation and during follow-up, included prolactin, total testosterone, LH, FSH, morning cortisol, TSH and FT4 measurements. Data regarding cabergoline treatment, testosterone replacement, surgical therapy, and radiotherapy were collected. During clinic visits, patients were asked about decreased libido and/or erectile dysfunction: positive response was classified as “sexual dysfunction”.

HH was defined as low serum total testosterone (< 2.8 ng/mL) with low or inappropriately normal LH levels. HH persistence was defined as HH at the end of follow-up, after at least 12 months of cabergoline treatment, and a minimum of 6 months interval between prolactin normalization and end of follow-up testosterone measurement. Central adrenal insufficiency was defined as 9:00 a.m. cortisol value below 100 nmol/L or below 450 nmol/L following ACTH stimulation. Central hypothyroidism was defined as low or inappropriately normal TSH levels in the presence of low FT4 levels.

Treatment and follow-up protocol

Cabergoline treatment was initiated at a weekly dose of 0.5 mg, or at a higher weekly dose of 1 mg in cases of baseline prolactin levels ≥ 1000 ng/mL. Doses were up-titrated every 2–3 months according to prolactin levels, as needed, until they reached either normalization or plateau.

Patients that suffered from HH persistence for ≥ 6 months following prolactin normalization and remained symptomatic were offered testosterone therapy.

The RMC pituitary clinic’s treatment and follow-up protocol for this cohort of male macroprolactinoma is available in a previously published article [7].

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Biochemical evaluation

Serum prolactin levels were measured by immunometric assay (Immulite 2000; Siemens), which has a sensitivity of 0.15 ng/mL. The intra-assay coefficients of variation (CVs) for prolactin 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 2–20 ng/mL. Levels ≥ 200 ng/mL were calculated after appropriate serum dilutions.

Reference total testosterone levels for men in our laboratory are 2.8–9.6 ng/mL.

Reference levels for other laboratory tests were determined according to each kit manufacturer’s instructions.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 27.0 (IBM Corp., Armonk, NY).

Continuous variables were presented by Mean (SD) or Median (IQR) as appropriate. Dichotomous variables were presented by N (%).

In order to compare the baseline characteristics of included and excluded patients, analysis of variance (ANOVA) was used for normally distributed continuous variables. Kruskal–Wallis test was used for non-normal continuous variables, and Chi-square test was used for categorical variables.

The study cohort included 2 groups: men that achieved eugonadism at the end of follow-up, and men that remained hypogonadal. In the event of testosterone replacement, the last testosterone, LH and FSH measurements recorded just before replacement treatment were documented as end of follow-up measurements, in a “last observation carried forward” manner.

Univariate analyses exploring associations between baseline characteristics and HH persistence were performed. An independent-samples T test was used to compare the values of normally distributed continuous variables among the two groups. Mann–Whitney test was used for non-normal continuous variables.

Relative risk (RR) was calculated for dichotomous variables to describe the strength of the relationship between the categorical risk factors and HH persistence.

Correlations between normally distributed continuous variables were performed using Pearson’s R. Spearman’s Rho was used for correlations between non-normal continuous variables.

Multivariate logistic regression model for HH persistence was developed to explore the relative contributions of the predicting factors. Continuous variables were included in the model if the p value was less than 0.05. Dichotomous variables were included in the model if the RR was 2.5 or greater and the p value was less than 0.05. Two-sided p value less than 0.05 were considered statistically significant.

Results

The study was performed between February 1993 and December 2020. During the study period we identified 103 male patients with macroprolactinoma. Fourteen patients were excluded due to eugonadism at presentation (Fig. 1). Thirty-one patients were excluded because they either did not reach normoprolactinemia, had surgery and/or radiotherapy, or had less than 12 months of follow-up (Fig. 1). Fifty-eight male patients with HH at presentation, who received cabergoline treatment with subsequent prolactin normalization were included in the study. The baseline characteristics of excluded patients are presented in the supplementary material (Table S1).

Entire cohort

The cohort included 58 male patients with HH at presentation, who received cabergoline treatment with subsequent prolactin normalization (Fig. 1).

The median baseline prolactin levels were 1154 ng/mL (IQR 505–2663 ng/mL), with mean prolactinoma (maximal) diameter at presentation of 25.9 ± 14.8 mm, and a mean baseline total testosterone of 1.5 ± 0.8 ng/mL. The mean baseline LH levels were 1.5 ± 1.4 mIU/mL. Twelve men (21%) suffered from HH persistence at the end of follow-up, while 46 men (79%) achieved eugonadism.
At diagnosis, VFDs were documented in 9 (16%) patients. Hypopituitarism (i.e., central adrenal insufficiency and/or central hypothyroidism) was diagnosed in 8 (14%) patients.

**Baseline characteristics of men with and without HH persistence**

The age at diagnosis did not differ between the two groups (Table 1).

Median baseline prolactin levels were 2003 ng/mL (IQR 474–6593 ng/mL) in the group of men with HH persistence and 1014 ng/mL (478–2416 ng/mL) in the group of men that achieved eugonadism (p = 0.17).

Mean prolactinoma (maximal) diameter was larger in men with HH persistence (34.6 ± 18.9 vs 23.7 ± 12.8 mm, p = 0.02, Table 1).

Mean baseline testosterone was 0.7 ± 0.6 and 1.6 ± 0.7 ng/mL (p < 0.01), LH was 0.4 ± 0.2 and 1.8 ± 1.5 mIU/mL (p < 0.01), and FSH 0.9 ± 0.7 and 3.4 ± 2.9 mIU/mL (p < 0.01) in men with and without HH persistence, respectively (Table 1).

Cavernous sinus invasion was evident in 10 (83%) and 34 (74%) men with and without HH persistence, respectively (RR 1.6; 95% CI 0.4–6.4, Table 1). Suprasellar extension was evident in 10 (83%) patients with HH persistence vs 15 (33%) men without HH persistence (RR 6.6; 95% CI 1.6–27.8, Table 1).

**Initial response to cabergoline treatment in men with and without HH persistence**

Prolactin and testosterone levels were evaluated in 55 patients after 3 months of treatment (12/12 and 43/46 in the patients with HH persistence and those that achieved eugonadism, respectively).

Median prolactin levels after 3 months of cabergoline treatment were 6.5 ng/mL (IQR 4.1–63.0 ng/mL) in the group of men with HH persistence and 16 ng/mL (6.0–43.0 ng/mL) in men that achieved eugonadism (p = 0.55). After 3 months of treatment, prolactin levels decreased by 94.9 ± 8.9 and 94.2 ± 13.4 percent (p = 0.51), respectively.

Mean testosterone levels after 3 months of cabergoline treatment were 0.9 ± 0.7 and 2.5 ± 1.1 ng/mL (p < 0.01) in men with and without HH persistence, respectively. Testosterone levels increased by 51.9 ± 91.4 percent and 97.5 ± 234.2 (p = 0.50), respectively.

**Table 1** Baseline characteristics of male patients with macroprolactinoma that achieved normal prolactin levels with cabergoline treatment, with and without hypogonadotropic hypogonadism persistence

| Variable                                      | Without HH persistence (n=46) | HH persistence (n=12) | RR | 95% confidence interval | p value |
|-----------------------------------------------|------------------------------|-----------------------|----|-------------------------|---------|
| Age at diagnosis, years—mean (SD)             | 49.5 (13.6)                  | 48.3 (8.6)            | –  | –                       | 0.76    |
| Prolactin, ng/mL—median (IQR)                 | 1014 (478–2416)              | 2003 (474–6593)       | –  | –                       | 0.17    |
| Adenoma maximal diameter, mm—mean (SD)        | 23.7 (12.8)                  | 34.6 (18.9)           | –  | –                       | 0.02    |
| Testosterone, ng/mL—mean (SD)                 | 1.6 (0.7)                    | 0.7 (0.6)             | –  | –                       | <0.01   |
| Luteinizing hormone, mIU/mL—mean (SD)a        | 1.8 (1.5)                    | 0.4 (0.3)             | –  | –                       | <0.01   |
| Follicle-stimulating hormone, mIU/mL—mean (SD)a | 3.4 (2.9)                  | 0.9 (0.7)             | –  | –                       | <0.01   |
| Cavernous sinus invasion—n (%)                 | 34 (74%)                     | 10 (83%)              | 1.6| 0.4–6.4                 | 0.07    |
| Suprasellar extension—n (%)                   | 15 (33%)                     | 10 (83%)              | 6.6| 1.6–27.8                | <0.01   |
| Visual field defect—n (%)                     | 4 (9%)                       | 5 (42%)               | 3.8| 1.5–9.3                 | 0.01    |
| Hypopituitarism—n (%)b                        | 2 (4%)                       | 6 (50%)               | 6.3| 2.6–14.8                | <0.01   |
| Central hypothyroidism—n (%)                  | 2 (4%)                       | 5 (42%)               | –  | –                       | <0.01   |
| Central adrenal insufficiency—n (%)           | 1 (2%)                       | 3 (25%)               | –  | –                       | 0.03    |
| Sexual dysfunction—n (%)                      | 36 (82%)                     | 12 (100%)             | NA | NA                      | 0.18    |

NA means not applicable

aBaseline LH and FSH measurements were performed in 42/46 and 9/12 of the patients (n = 51). The remaining seven patients completed LH and FSH measurements later.

bCentral adrenal insufficiency and/or central hypothyroidism, in addition to HH.
Baseline testosterone levels strongly correlated with testosterone levels after 3 months of treatment ($R = 0.53$, $p < 0.01$).

**Long term response to cabergoline treatment in men with and without HH persistence**

Our cohort of 58 men was followed for a median of 5.6 years (IQR 3.0–10.7 years). The mean weekly maximal cabergoline dose was $2.0 \pm 1.1$ and $1.6 \pm 1.7$ mg in patients with and without HH persistence, respectively ($p = 0.05$, Table 2). The median time elapsed from medical treatment initiation to prolactin normalization was $5.0$ (IQR 3.2–10.5) and $5.0$ (IQR 2.7–11.3) months in patients with and without HH persistence, respectively ($p = 0.86$, Table 2).

End of follow-up prolactin levels and adenoma (maximal) diameter were not significantly different between patients in the two groups (Table 2).

In accordance with the pre-determined allocation, total testosterone levels at the end of follow-up were lower in the group of men with HH persistence: $1.0 \pm 0.6$ compared to $4.6 \pm 1.1$ ng/mL (Table 2). LH was $1.0 \pm 1.0$ vs $4.1 \pm 2.7$ mIU/mL ($p < 0.01$), and FSH was $2.3 \pm 2.3$ vs $6.2 \pm 4.3$ mIU/mL ($p = 0.02$) in men with and without HH persistence, respectively, at the end of follow-up (Table 2). We found a linear correlation between baseline testosterone levels and end of follow-up testosterone levels (Fig. 2).

In the group of men that achieved eugonadism with cabergoline, the median time elapsed from prolactin normalization to eugonadism restoration was 2.9 months (IQR 0.1–6.0 months). In this group of 46 men, after normoprolactinemia was achieved 36 (78%) men normalized their testosterone levels within the first 6 months, and 42 (91%) men normalized testosterone within the first 12 months.

In the group of men that suffered HH persistence, the median time elapsed from prolactin normalization to testosterone replacement initiation was 16.4 months (IQR 10.0–19.9 months).

At the end of follow-up, residual VFDs were evident in 2/5 (40%) and 1/4 (25%) men with and without HH persistence, respectively (Table 2).

Residual pituitary hormone deficiency was demonstrated in 5/6 (83%) and 2/2 (100%) men with and without HH persistence, respectively (Table 2). Only two men in the cohort (both suffered HH persistence) accomplished full recovery of hypothalamic–pituitary–adrenal axis.

No sexual dysfunction improvement was noted in those with HH persistence, while 91% of men who achieved eugonadism experienced sexual improvement ($p < 0.01$, Table 2).

**Independent predictors of HH persistence**

Baseline testosterone levels had a significant correlation with both LH levels ($R = 0.45$, $p = 0.01$) and FSH levels ($R = 0.33$, $p = 0.01$). VFD correlated well with suprasellar extension ($R = 0.49$, $p = 0.01$).

### Table 2  Long term response to cabergoline treatment

| Variable                              | Without HH persistence (n = 46) | HH persistence (n = 12) | p value |
|---------------------------------------|--------------------------------|------------------------|---------|
| Cabergoline dose, mg/week—mean (SD)  | 1.6 (1.7)                      | 2.0 (1.1)              | 0.05    |
| Time to prolactin normalization, months—median (IQR) | 5.0 (2.7–11.3) | 5.0 (3.2–10.5) | 0.86    |
| Prolactin, ng/mL—median (IQR)        | 7.9 (4.1–13.3)                 | 5.8 (3.7–8.8)          | 0.17    |
| Testosterone levels, ng/mL—mean (SD)$^a$ | 4.6 (1.1)                     | 1.0 (0.6)              | –       |
| Luteinizing hormone, mIU/mL—mean (SD)$^{ab}$ | 4.1 (2.7)                | 1.0 (1.0)              | <0.01   |
| Follicle-stimulating hormone, mIU/mL—mean (SD)$^{ab}$ | 6.2 (4.3)                  | 2.3 (2.3)              | 0.02    |
| Adenoma maximal diameter, mm—mean (SD) | 12.1 (7.4)                  | 12.8 (11.7)            | 0.78    |
| Reduction in adenoma maximal diameter—% (SD) | 46.7 (26.1)            | 63.0 (32.0)            | 0.07    |
| Residual visual field defect—n (%)    | 1/4 (25%)                     | 2/5 (40%)              | NS      |
| Residual pituitary hormone deficiency—n (%) | 2/2 (100%)                | 5/6 (83%)              | NS      |
| Central hypothyroidism—n (%)         | 2/2 (100%)                   | 5/5 (100%)             | NS      |
| Central adrenal insufficiency—n (%)  | 1/1 (100%)                   | 1/3 (33%)              | NS      |
| No sexual dysfunction improvement—n (%) | 3/34 (9%)                   | 10/10 (100%)           | <0.01   |

NS means no statistical significance (i.e., insufficient sample size)

$^a$In men treated with testosterone replacement: the last Testosterone, LH and FSH measurements recorded just before replacement treatment were documented as their end of follow-up measurements, in a “last observation carried forward” manner

$^b$Only 31/46 and 7/12 end of follow-up measurements were available (n = 38)

$^c$Data was available for 34/46 and 10/12 subjects (n = 44)
The multivariate logistic regression model (Table 3) demonstrated that hypopituitarism (OR 10.1; 95% CI 1.10–101.94), VFD (OR 9.9; 95% CI 1.07–92.33), and low baseline testosterone levels (OR 0.5; 95% CI 0.29–0.93) were independent predictors of HH persistence in men with macroprolactinoma that reached prolactin normalization with cabergoline treatment. Adenoma (maximal) diameter (OR 1.0; 95% CI 0.96–1.07) did not predict HH persistence in the multivariate model. Area under curve (AUC) of the receiver operating curve (ROC) was 0.906.

Baseline testosterone levels below 1.5 ng/mL together with either VFD or hypopituitarism, demonstrated a sensitivity of 75% and specificity of 93.5% to predict HH persistence.

Discussion

In our cohort of men with macroprolactinoma and hypogonadism at presentation who reached normoprolactinemia with cabergoline treatment, 21% showed HH persistence. This is the first study to report hypopituitarism and VFD (reflecting significant tumor mass effect) as independent predictors of HH persistence in men with macroprolactinoma. We found substantial correlations between baseline LH and FSH levels with testosterone levels (reflecting central functional modification) and identified low baseline testosterone as an independent predictor of HH persistence.

Previous studies (Table 4), with similar study designs, investigated the prevalence of HH persistence. Several studies have identified clinical factors associated with HH persistence (Table 4). In 2000, Pinzone et al. [6] retrospectively evaluated 27 men with macroprolactinoma and found that 93% of men had hypogonadism at presentation, with 48% suffering HH persistence after 4.4 years. They reported no age difference between men with and without HH persistence. Sibal et al. [8] demonstrated gonadal axis dysfunction in 27 out of 35 men (77%) and recovery of function in 16 out of 26 (62%) men, under medical treatment with dopamine agonists. In 2006, De rosa et al. [10] prospectively evaluated 50 men with macroprolactinomas (76% had baseline HH) and found that 18 out of 38 (47%) patients that achieved normoprolactinemia had HH persistence after 6 months of cabergoline treatment. The investigators demonstrated that

Table 3 Multivariate logistic regression model for hypogonadotropic hypogonadism persistence in male patients with macroprolactinoma that achieved normal prolactin levels with cabergoline treatment

| Variable                                | OR   | 95% confidence interval | p value |
|-----------------------------------------|------|-------------------------|---------|
| Hypopituitarisma                        | 10.1 | 1.10–101.94             | 0.04    |
| Visual field defect                     | 9.9  | 1.07–92.33              | 0.04    |
| Baseline testosterone, ng/mL            | 0.5  | 0.29–0.93               | 0.02    |
| Adenoma (maximal) diameter, mm          | 1.0  | 0.96–1.07               | 0.56    |

Area under curve (AUC) of the receiver operating curve (ROC): 0.906

*aCentral adrenal insufficiency and/or central hypothyroidism, apart from HH*
higher basal prolactin levels, larger tumors, and lower baseline testosterone levels were associated with HH persistence after 6 months. Karavitaki et al. [17] investigated 10 men (9 had gonadal axis dysfunction) treated with cabergoline for 2 years, with HH persistence seen in 5 out 9 men (56%). Men who achieved eugonadism with cabergoline, did so within the first year of treatment.

In 2020, Sehemby et al. [11] studied a cohort of 30 men with macroprolactinomas and hypogonadism. All included men achieved normoprolactinemia with cabergoline therapy, and yet 73% of men had HH persistence at the end of the study period (median follow-up of 2 years). In this study of well selected population, higher baseline prolactin levels and larger tumor size were found to be predictors of HH persistence, both factors reflect tumor aggressiveness. The authors provided cutoffs for tumor size smaller than 32 mm (sensitivity and specificity of 75% and 63.6%) and basal prolactin levels below 2098 ng/mL (87.5% and 77.3%) for HH reversal prediction. It should be noted that these cutoffs will probably yield lower specificity in populations of other ethnical origin, with less aggressive prolactinomas and with lower rates of HH persistence: in our cohort, tumor size < 32 mm had 82.6% sensitivity and 50% specificity, and prolactin < 2098 ng/mL had 71.7% sensitivity and 50% specificity for HH reversal prediction.

In their study, Sehemby et al. [11] demonstrated selective suppression of the LH-testosterone axis (without suppression of the FSH-inhibin B axis) and thus they suggest that “chronic functional modification” of the hypothalamus, and not gonadotroph cell damage, is the biological mechanism of persistent HH.

A study published by Voica et al. [20] retrospectively evaluated 26 cases of hypogonadal men harboring prolactinoma (only 20 had macroprolactinoma). Sixteen men (62%) suffered from HH persistence. High baseline prolactin levels, large tumor, and lower baseline testosterone levels were associated with HH persistence.

In our cohort, lower baseline testosterone, LH and FSH levels were associated with HH persistence (Table 4). Prolactin levels were lower in men without HH persistence (Table 4). On one hand, these observations suggest that the impairment of the gonadal axis is primarily functional and derives from the known effect of high prolactin levels over the hypothalamus. On the other hand, we found

| Author          | Year | Male macroprolactinoma, N | Baseline HH, n (%) | Cabergoline, n (%) | TSS/RT, n (%) | Prolactin normalization, n (%) | HH persistence, n (%) | Length of FU in years, median | HH persistence predictors identified |
|-----------------|------|----------------------------|--------------------|-------------------|---------------|-------------------------|---------------------|---------------------------------|-----------------------------------|
| Pinzone et al.  | 2000 | 34                         | 25/27 (93%)        | 10 (29%)          | 0 (0%)        | 27 (79%)                | 12/25 (48%)          | 4.4                             |                                    |
| Sibal et al.    | 2002 | 35                         | 27/35 (77%)        | NA                | 0 (0%)        | 29 (83%)                | 16/26 (62%)          | 2.6                             | High baseline PRL, large tumor size, lower T levels |
| De rosa et al.  | 2006 | 50                         | 38/50 (76%)        | 50 (100%)         | 0 (0%)        | 38 (76%)                | 18/38 (47%)          | 0.5                             |                                    |
| Karavitaki et al. | 2013 | 12                         | 9/10 (90%)        | 12 (100%)         | 2 (17%)       | 11 (92%)                | 5/10 (50%)           | 4.2                             | High baseline PRL, large tumor size |
| Sehemby et al.  | 2020 | 30                         | 30/30 (100%)       | 30 (100%)         | 0 (0%)        | 30 (100%)               | 22/30 (73%)          | 2.0                             | High baseline PRL, large tumor size |
| Voica et al.    | 2021 | 26a                        | 26/26 (100%)       | NA                | NA            | 20/26 (77%)             | 16/26 (62%)          | NA                              | High baseline PRL, large tumor size |
| Present study   | 2022 | 58                         | 58/58 (100%)       | 58 (100%)         | 0 (0%)        | 58/58 (100%)            | 12/58 (21%)          | 5.6                             | High baseline PRL, hypopituitarism, visual field defects |

HH hypogonadotropic hypogonadism, TSS trans-sphenoidal surgery, RT radiotherapy, FU follow-up, PRL prolactin, T testosterone, NA not available

*aSix men had microprolactinoma
hypothesis that hypopituitarism and VFD reflect both tumor size and tumor growth rapidity (the two components that constitute the destructive mass effect), and this may explain why hypopituitarism and VFD predict hypogonadism persistence better than tumor size alone. Thus, to damage the normal pituitary tissue and/or the optic nerves, the tumor should not only be large enough, but also grow fast enough. This may explain why approximately 60% of patients with giant macroadenomas do not develop hypopituitarism and more than 40% do not develop VFD [7, 21].

After normoprolactinemia was achieved, in the group of 46 men without HH persistence, we found that 36 men (78%) in our cohort normalized their testosterone levels within the first 6 months, and 42 men (91%) accomplished eugonadism within the first year. One patient demonstrated recovery of the gonadal axis after as long as 4.5 years. Accordingly, it is possible that a limited number of patients may benefit from gonadal axis function reassessment, even after a long period of axis suppression. In order to aid in the decision of testosterone replacement initiation, our data suggest that men who present with testosterone levels below 1.5 ng/mL, along with either VFD or hypopituitarism are more likely to remain hypogonadal despite prolactin normalization (75% sensitivity, 93.5% specificity) and may benefit from testosterone treatment.

Although baseline HH is associated with a more aggressive disease (Table S1), our data suggest that the long-term outcomes in men with and without HH persistence are comparable, including prolactin normalization and tumor shrinkage (Table 2). Accordingly, the mean time elapsed from medical treatment initiation to prolactin normalization was identical (5 months) in the two groups. As anticipated, in accordance with the low LH and the pre-specified testosterone levels, men with HH persistence did not demonstrate sexual function improvement (Table 2).

The present study has many strengths, including the meticulous data collection, a uniform treatment protocol, long-term follow-up, and the ability to ascertain several predictors of HH persistence, two of them (VFD and hypogonadism) have not been previously reported. This study has a number of limitations. Because of its retrospective nature, outcomes reported by patients were subject to reporting bias. Baseline LH and FSH measurements were missing for seven patients, and yet all patients completed LH and FSH measurements during follow-up (all were compatible with a diagnosis of hypogonadotropic hypogonadism). Many patients were not included in the main analysis, due to the severity of their disease (Table S1). This may be the result of referral bias: as a tertiary referral center, our patients usually present with larger and more aggressive adenomas and require a more aggressive treatment approach. Another limitation is the lack of data regarding free testosterone or sex hormone-binding globulin levels. In addition, our protocol does not specify time intervals for serum testosterone measurements after the patients reached normal prolactin levels. This may have caused overestimation of time elapsed from prolactin normalization to eugonadism restoration.

In conclusion, in this cohort of men with macroadenoma that reached prolactin normalization with cabergoline treatment, 21% had HH persistence. We identified low baseline testosterone levels, visual field defect and pituitary hormone deficiency as independent predictors of HH persistence. We found that 91% of men accomplished eugonadism within the first year following prolactin normalization. These findings may support informed clinical decision-making regarding the initiation of testosterone replacement in men with macroadenomas.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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