Prolactin ≤ 1 ng/mL predicts macroprolactinoma reduction after cabergoline therapy

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Abstract

Objective: The association between prolactin level variation and prolactinoma size reduction remains unclear. This study aimed to determine the prolactin level cut-off predictive of a tumor size reduction.

Design: Retrospective cohort study.

Methods: We reviewed medical records of patients with prolactinoma who received primary cabergoline therapy and for whom complete data on pituitary hormone assays and sellar MRI at baseline and 3 months post treatment were available. We tested whether the certain prolactin level after 3 months post treatment predicted better response.

Results: Prolactin levels normalized in 109 (88.6%) of 123 included macroprolactinoma patients. The mean tumor size reduction was 22.9%, and patients in the lowest prolactin tertile (≤ 0.7) had the highest frequency of tumor size reductions of $\geq 20\%$ (73.7 vs 52.9% and 45.9% in tertiles 2 (>0.7 to 2.6) and 3 (>2.6 to 20), $P = 0.015$). Patients with prolactin levels ≤ 1 ng/mL exhibited larger tumor size reductions vs those with prolactin levels of 1–20 ($27.2 \pm 18.3\%$ vs $19.5 \pm 13.9\%$, $P = 0.014$), 1–10 ($19.3 \pm 13.7\%$, $P = 0.017$) and 1–5 ng/mL ($19.2 \pm 14.3\%$, $P = 0.039$). A multivariable logistic regression analysis revealed that a prolactin level ≤ 1 ng/mL at 3 months and high-dose cabergoline therapy were significantly associated with tumor size reductions of $\geq 20\%$ (odds ratio (OR): 2.8, 95% confidence interval (CI): 1.2–6.7, $P = 0.017$; OR: 2.0, 95% CI: 1.0–3.9, $P = 0.043$).

Conclusions: A prolactin level ≤ 1 ng/mL at 3 months after cabergoline treatment was correlated with a significant tumor size reduction in patients with macroprolactinoma. This finding may help clinical decision making when treating macroprolactinoma patients.

European Journal of
Endocrinology
(2020) 182, 177–183

Introduction

Prolactinomas are the most commonly occurring pituitary adenomas, accounting for approximately 40% of all pituitary tumors and 50–60% of all functional pituitary tumors (1). These tumors cause headaches, visual dysfunction, hypopituitarism, and hyperprolactinemia (2). Patients with prolactinoma typically exhibit the clinical features of hyperprolactinemia, including gonadal dysfunction, amenorrhea, and galactorrhea.

Serum prolactin level normalization and tumor shrinkage are the major goals of prolactinoma treatment.

The first line of therapy involves medical management with dopamine agonists such as bromocriptine and cabergoline. Surgical resection is generally reserved for patients who are unresponsive or intolerant to medical therapy. Cabergoline, a specific D2 receptor agonist, is the first choice of treatment because of its superior efficacy and better tolerability (3). The recommended cabergoline dosage for initiation is 0.25–0.5 mg twice a week, whereas the usual weekly maintenance doses range from 0.25 to 3.0 mg (4).

In a previous study, treatment with 0.125–1.0 mg cabergoline twice weekly for 12–24 months resulted in the normalization of prolactin levels in 95% of patients with microprolactinoma (5). In another study of macroprolactinoma, normoprolactinemia was achieved in 81% of patients receiving 0.25–2 mg cabergoline weekly (6). Cabergoline treatment is very effective, and response assessments based on the tumor volume reduction and prolactin normalization after 3 months of treatment are useful for predicting long-term responses and resistance to cabergoline (7). However, prolactin levels may decrease below the normal range even after normalization following 3 months of cabergoline treatment.

Differences in tumor size reduction within the prolactin normalization cut-off values have not yet been determined. Therefore, this study aimed to evaluate the potential use of prolactin cut-off values to predict tumor size reductions in patients with macroprolactinoma.

Patients and methods

Patients

We reviewed the medical records of patients with prolactinoma who were treated with cabergoline as a primary drug therapy at Severance Hospital between November 2011 and June 2017. A diagnosis of prolactinoma was made if a patient presented with a serum prolactin level above the normal range and pituitary adenomas on sellar MRI (8). Before confirming a prolactinoma diagnosis, secondary causes of hyperprolactinemia were ruled out by assessing the clinical history, including current medications, physical examination findings, pregnancy tests, routine biochemical analysis with thyroid function tests, and neuroimaging.

To evaluate the relationships among parameters, we included patients for whom the following information was available: complete pituitary hormone assay data and sellar MRI findings at baseline, follow-up prolactin assay data, and sellar MRI findings at 3 months after cabergoline treatment. We excluded patients who underwent transsphenoidal adenomectomy before the third month of cabergoline treatment. Accordingly, 217 of 221 identified patients were enrolled (Fig. 1). This study was conducted in accordance with the 1964 Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital (No. 4-2019-0400). The requirement for informed consent was waived because of the retrospective nature of this study.

Figure 1

Flow chart of the study. CAB, cabergoline; MRI, magnetic resonance imaging; PRL, prolactin; TSA, transsphenoidal adenomectomy; 3m f/u, 3-month follow-up.

Treatment and response assessment

In all cases, oral cabergoline was initiated at a low dose (0.5–1 mg/week), and the dosage was gradually increased to a maintenance dose within 2–4 weeks (7). The latter dose was maintained for 3 months after treatment initiation to ensure a sufficient period of drug exposure.

A response evaluation was conducted after 3 months. The serum prolactin levels were measured using chemiluminescence immunoassay using commercial kits (Beckman Coulter, Brea, CA, USA). The lower limit of detection for the prolactin assay was 0.25 ng/mL, and if the prolactin values were not as high as expected, the assay was repeated after a 1:100 serum sample dilution to overcome a potential hook effect. The within-run and total coefficients of variation for prolactin concentrations were 3.66 and 3.77%, respectively. Prolactin normalization was defined as the achievement of a concentration <20 ng/mL. The lower limit of normal prolactin level was 5 ng/mL, and the lower limit of detectable prolactin level was 1 ng/mL. These criteria were used to classify patients (8). Although our assay kit is more sensitive, we used generally accepted criteria.

Sellar MRI was performed using a 1.5-Tesla (Signa; General Electric, Minneapolis, MN, USA) or 3.0-Tesla system (Achieva; Philips, Best, The Netherlands). The maximum tumor diameter was measured and used to classify prolactinomas as microprolactinoma (<10 mm) or macroprolactinoma (≥10 mm) (8). A tumor size reduction was calculated as the (initial tumor size – tumor size after 3 months of cabergoline treatment)/initial tumor size. We set the tumor size reduction cut-off value according to the mean size reduction of macroprolactinoma patients

who achieved prolactin normalization after 3 months of cabergoline treatment.

Statistical analysis

SPSS Statistics version 23 (IBM Corp.) was used for all statistical analyses. Categorical variables are presented as numbers and percentages. Continuous variables are expressed as means $\pm$ s.d. Statistical comparisons of the mean values were performed using Student's *t*-test, and group comparisons were performed using the χ^2 test or linear-by-linear association, as appropriate. A multivariable logistic regression analysis was used to determine variables independently associated with tumor size reductions ($\geq 20\%$) based on observed characteristics of patients (age (years), sex (female), initial tumor size (mm), cabergoline dose (mg/week), and prolactin ≤ 1 ng/mL).

Results

Patient characteristics

The characteristics of the 217 included patients are shown in Table 1. The patients had a mean age of 35 years at diagnosis, and most (82.0%) were female. After 3 months of cabergoline treatment, 92.2% of the patients achieved prolactin normalization. Ninety-four and 123 patients had microprolactinoma and macroprolactinoma, respectively. Patients in the macroprolactinoma group had an older mean age than those in the microprolactinoma group. All patients with microprolactinoma were female. The serum prolactin levels at the baseline and after 3 months of treatment were higher in the macroprolactinoma group than in the microprolactinoma group. Patients in the macroprolactinoma group received a higher cabergoline dose than those in the microprolactinoma group. Moreover,

96.8% of patients in the microprolactinoma group and 88.6% of those in the macroprolactinoma group achieved prolactin normalization. However, the percentage of size reduction was greater in the macroprolactinoma group than in the microprolactinoma group. As it is difficult to measure exact size changes in small tumors, our further evaluations included only patients with macroprolactinoma patients who achieved prolactin normalization.

Tumor size reduction according to prolactin level

Next, we compared tumor size reductions within the prolactin normalization cut-off value after 3 months of cabergoline treatment. Macroprolactinoma patients who achieved prolactin normalization had a mean size reduction of 22.9%. Simple linear regression analysis was performed to evaluate the relationship between the prolactin level and tumor size reduction; however, no significant linear relationship was observed between these variables ($r = -0.1$, $\beta = -0.5$, 95% CI: -1.3 to 0.2). However, when we divided patients who achieved prolactin normalization into tertiles and set the tumor size reduction cut-off value at 20% according to the mean size reduction, we observed a linear relationship between the prolactin level and tumor size reduction (tertiles 1 vs 2 vs 3: 73.7% vs 52.9% vs 45.9%, $P = 0.015$; Table 2).

Tumor size reduction classified by a prolactin level cut-off of 5 ng/mL

We classified macroprolactinoma patients who achieved prolactin normalization after 3 months of cabergoline treatment into two groups according to their prolactin level relative to a cut-off of 5 ng/mL (Supplementary Table 1, see section on [supplementary materials](#) given at the end of this article). Patients in the low (≤ 5 , $n = 82$) and

Table 1 Characteristics of the study patients.

	Total ($n = 217$)	Microprolactinoma ($n = 94$)	Macroprolactinoma ($n = 123$)	P value
Age (years)	34.6 $\pm$ 10.7	31.9 $\pm$ 7.3	36.7 $\pm$ 12.3	<0.001
Female, n (%)	178 (82.0)	94 (100)	84 (68.3)	<0.001
Prolactin (ng/mL)				
Initial	490.2 $\pm$ 1344.7	115.9 $\pm$ 72.8	776.3 $\pm$ 1734.0	<0.001
After 3 months	8.7 $\pm$ 26.4	4.1 $\pm$ 7.4	12.2 $\pm$ 34.1	0.012
Tumor size (mm)				
Initial	13.7 $\pm$ 10.4	7.3 $\pm$ 1.5	18.6 $\pm$ 11.6	<0.001
After 3 months	10.9 $\pm$ 9.2	6.1 $\pm$ 1.8	14.6 $\pm$ 10.7	<0.001
Size reduction (%)	19.5 $\pm$ 17.7	16.1 $\pm$ 19.0	22.1 $\pm$ 16.2	0.013
PRL normalization, n (%)	200 (92.2)	91 (96.8)	109 (88.6)	0.039
CAB dose (mg/week)	2.2 $\pm$ 0.7	2.0 $\pm$ 0.6	2.4 $\pm$ 0.8	<0.001

CAB, cabergoline; PRL, prolactin.

Clinical Study	D Kim and others	PRL cut-offs and tumor size reduction	182:2	180
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Table 2 Percentage of cases with size reductions of $\geq 20\%$ among macroprolactinoma patients who achieved prolactin normalization after 3 months of cabergoline treatment (classified by tertiles).

	1st tertile (PRL ≤ 0.7 , $n = 38$)	2nd tertile (>0.7 to 2.6 , $n = 34$)	3rd tertile (>2.6 to 20 , $n = 37$)	P value
Size reduction				
<20%	10 (26.3%)	16 (47.1%)	20 (54.1%)	0.015
$\geq 20\%$	28 (73.7%)	18 (52.9%)	17 (45.9%)	

PRL levels are given in units of ng/mL.
PRL, prolactin.

high prolactin groups (>5 – 20 ng/mL, $n=27$) had a similar mean age at diagnosis and proportion of women and did not differ in terms of the initial serum prolactin level and initial tumor size. Moreover, the two groups received similar cabergoline doses and did not differ in the degree of tumor size reduction after 3 months of cabergoline treatment.

Tumor size reduction classified using a prolactin level cut-off of 1 ng/mL

Next, we classified macroprolactinoma patients who achieved prolactin normalization after 3 months of cabergoline treatment into two groups according to a prolactin level cut-off level of 1 ng/mL. Moreover, the low (≤ 1 , $n=49$) and high prolactin groups (>1 – 20 ng/mL, $n=60$) had a similar mean age at diagnosis and proportion of women (Table 3) and did not differ in terms of the initial serum prolactin level, initial tumor size, and cabergoline dose. However, the two groups differed significantly in the degree of size reduction ($27.2 \pm 18.3\%$ vs $19.5 \pm 13.8\%$, $P=0.014$; Fig. 2A). As a wide range of prolactin levels was

observed in the high group, we narrowed the range in this to prolactin levels of >1 to 10 ($n=50$) and >1 to 5 ng/mL ($n=33$). For both narrowed high groups, the degrees of size reduction differed significantly from those in the low group (≤ 1 ng/mL, $n=49$; $27.2 \pm 18.3\%$ vs $19.3 \pm 13.7\%$, $P=0.017$ and $27.2 \pm 18.3\%$ vs $19.2 \pm 14.3\%$, $P=0.039$, respectively; Fig. 2B and C). When we set the tumor size reduction cut-off value at 20%, less than half of the patients in the high group achieved this outcome after 3 months of cabergoline treatment. However, more than 70% of patients in the low group achieved a tumor size reduction of $\geq 20\%$ (Supplementary Table 2).

A multivariable logistic regression analysis revealed that the odds ratio (OR) for size reductions of $\geq 20\%$ increased significantly in cases that received a high cabergoline dose (OR: 2.0, 95% CI: 1.0–3.9, $P=0.043$) and in patients whose prolactin levels decreased to <1 ng/mL after 3 months of cabergoline treatment (OR: 2.8, 95% CI: 1.2–6.7, $P=0.017$; Table 4). Therefore, a reduction in the prolactin level to <1 ng/mL was correlated with a significant tumor size reduction in patients with macroprolactinoma, even if prolactin levels had normalized after 3 months of cabergoline treatment.

Discussion

Prolactinoma is the most commonly occurring pituitary adenoma observed in clinical practice (1). In such settings, cabergoline treatment is an effective, safe, and well-tolerated approach. A response assessment based on the tumor volume reduction and prolactin normalization after 3 months of treatment is useful for predicting the long-term response and resistance to cabergoline (7). However, differences within the prolactin normalization

Table 3 Macroprolactinoma patients who achieved prolactin normalization after 3 months of cabergoline treatment, classified using a prolactin cut-off value of 1 ng/mL.

	Total ($n = 109$)	Low group (PRL ≤ 1 , $n = 49$)	High group (>1 to 20 , $n = 60$)	P value
Age (years)	36.1 ± 11.9	38.3 ± 12.0	34.4 ± 11.7	0.088
Female, n (%)	79 (72.5)	35 (71.4)	44 (73.3)	0.825
Prolactin (ng/mL)				
Initial	702.9 ± 1725.4	902.9 ± 2380.8	539.6 ± 881.7	0.315
After 3 months	3.3 ± 4.4	0.4 ± 0.3	5.7 ± 4.7	<0.001
Tumor size (mm)				
Initial	17.4 ± 10.4	18.2 ± 10.2	16.7 ± 10.6	0.470
After 3 months	13.4 ± 9.4	13.3 ± 8.8	13.6 ± 9.9	0.884
Size reduction (%)	22.9 ± 16.4	27.2 ± 18.3	19.5 ± 13.9	0.014
CAB dose (mg/week)	2.3 ± 0.8	2.5 ± 0.8	2.2 ± 0.7	0.076

CAB, cabergoline; PRL, prolactin.

Figure 2

Tumor size reductions according to the prolactin levels at 3 months. (A) Prolactin level ≤ 1 ($n = 49$) vs > 1 to 20 ng/mL ($n = 60$). (B) Prolactin level ≤ 1 ($n = 49$) vs > 1 to 10 ng/mL ($n = 50$). (C) Prolactin level ≤ 1 ($n = 49$) vs > 1 to 5 ng/mL ($n = 33$). PRL, prolactin. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-19-0753>.

cut-off value have not been identified previously. Here, we analyzed tumor size reductions within the prolactin normalization cut-off value and found that the degree of tumor size reduction was significantly greater in patients who achieved a prolactin level < 1 ng/mL after 3 months of cabergoline therapy. When we set the tumor size reduction cut-off value at 20%, more than 70% of patients who achieved a prolactin level < 1 ng/mL achieved this outcome. A multivariable logistic regression analysis revealed that a reduction in prolactin level to < 1 ng/mL after 3 months of cabergoline treatment was a significantly strong predictive factor of tumor reduction ($\geq 20\%$). This study is the first to compare differences within the prolactin normalization cut-off value as an early response to cabergoline in patients with prolactinoma.

When hyperprolactinemia is confirmed, a clinical and laboratory workup is necessary to identify the possible causes. After ruling out pregnancy, lactation, drug-related hyperprolactinemia, renal or hepatic insufficiency, and hypothyroidism, a sellar MRI is indicated (3). Although hyperprolactinemia with the existence of a pituitary adenoma is consistent with prolactinoma, it is not a sufficient factor for diagnosis. Prolactin production is normally inhibited by dopamine, a neurotransmitter released from the hypothalamus; therefore, hypothalamic or pituitary stalk disease may decrease this inhibition and

induce an increase in prolactin levels (9). It is difficult to discriminate prolactinoma from hyperprolactinemic nonfunctioning pituitary adenoma (NFPA), which may compress the pituitary stalk and cause hyperprolactinemia. Although serum prolactin levels can be reduced by dopamine agonist treatment in patients with NFPA, the majority of patients do not achieve tumor size reductions (10). In this study, most patients received a clinical diagnosis based on the nature of the disease, rather than pathologic confirmation, and some may have had NFPA. It is meaningful that a reduction in the prolactin level to < 1 ng/mL after 3 months of cabergoline therapy can predict a better response.

The differential diagnosis between prolactinoma and hyperprolactinemic NFPA is critical to the provision of an accurate medical treatment for prolactinoma or surgery for other tumors. In prolactinoma, a change in the serum prolactin level generally parallels a change in the tumor size. Therefore, a radiologically diagnosed large adenoma with a modestly elevated prolactin level would be suggestive of hyperprolactinemic NFPA rather than a prolactinoma, which would inhibit prolactin secretion from normal lactotrophs because of hypothalamic stalk dysfunction (11). We must also consider a potential hook effect when prolactin values are not as high as expected in a patient with a large macroadenoma. The association between the serum prolactin level and tumor size is not always consistent in patients with prolactinoma, and thus, hyperprolactinemic NFPA cannot be completely ruled out clinically. Therefore, a reduction in the prolactin level to < 1 ng/mL after 3 months of cabergoline therapy cannot completely replace sellar MRI.

Responses to dopamine agonists vary by the type of agonist, drug compliance, and drug dose. All the patients in this study received cabergoline as a primary drug. Cabergoline has a long half-life, which enables its oral administration only once or twice weekly. As this drug is associated with a lower incidence of unpleasant side effects than that associated with bromocriptine, the drug

Table 4 Multivariable logistic regression analysis of size reductions of $\geq 20\%$ in macroprolactinoma patients who achieved prolactin normalization after 3 months of cabergoline treatment, classified using a prolactin cut-off value of 1 ng/mL.

	Odds ratio	95% CI	P value
Age (years)	1.0	0.9–1.0	0.154
Sex (female)	0.7	0.2–2.0	0.480
Initial tumor size (mm)	1.0	0.1–1.1	0.935
CAB dose (mg/week)	2.0	1.0–3.9	0.043
Prolactin ≤ 1 ng/mL	2.8	1.2–6.7	0.017

CAB, cabergoline; CI, confidence interval.

compliance rate may be superior (11, 12). Higher doses are frequently more effective. However, the cabergoline dose did not differ between our study groups (mean difference: 0.3 mg/week, 95% CI: 0.0–0.6). The cabergoline doses ranged from 2 to 3 mg/week, which are usually effective for macroprolactinoma treatment (13). If the degree of tumor size reduction corresponds to the dose of cabergoline, we can consider the tumor to be highly responsive.

Prolactin is best known for its role in enabling mammals (usually females) to produce milk. It also plays essential roles in metabolism, immune system regulation, and pancreatic development (14). Although prolactin influences more than 300 separate processes, most people with low prolactin levels do not have any specific medical problems. However, some studies suggest that hypoprolactinemia is associated with ovarian dysfunction in women and sexual dysfunction and psychological or metabolic disturbances in men (15, 16, 17). Although further studies are needed to understand the directions of causality, the side effects associated with low prolactin levels should be considered during the treatment of prolactinoma.

Our study demonstrated that if the prolactin response to cabergoline treatment is more prominent with similar standard doses, a more significant tumor size reduction can be expected. Although high-dose cabergoline therapy may be more effective and necessary for overcoming resistance, the adverse effects associated with high doses of dopamine agonists should be considered. Although rare, these adverse events include cerebrospinal fluid leakage, chiasmal herniation, and pituitary apoplexy (18). Caution must be exercised in the protracted use of high-dose cabergoline because of the potential risk of cardiac valvular regurgitation (19).

This study had several limitations, including its retrospective single-center design, absence of pathological confirmation, and limitation of the patient sample to macroprolactinoma cases. Because of the retrospective design, the drug doses were determined by clinical decisions and not according to a standard study protocol. Cabergoline dose adjustments were performed based on periodic prolactin measurements and follow-up sellar MRI findings and not by dividing patients into groups. Therefore, we could not clarify long-term outcomes. In a previous study, cabergoline therapy intended to achieve a prolactin level below the lower limit of the normal range (as determined by the sum of the score) increased the likelihood of prolactinoma shrinkage after 24 months of treatment (20). Pathologic confirmation

was not possible in this study because medical therapy is the first line of treatment for patients with prolactinoma, whereas surgical treatment is indicated only for those exhibiting resistance or intolerance to dopamine agonists (3). Furthermore, we analyzed the prolactin cut-offs in patients with macroprolactinoma, although clinically, cabergoline treatment is maintained even in the absence of significant tumor size reductions in patients with microprolactinoma. Therefore, the clinical application of our study is limited to patients with macroprolactinoma.

The main strength of our study was the enrollment of a relatively large number of patients with a rare disease who received single-agent therapy. Currently, cabergoline is the first choice of drug therapy because it is associated with fewer side effects and more effectively normalizes prolactin levels, compared with bromocriptine. Our study suggests that a prolactin level ≤ 1 ng/mL after 3 months of cabergoline treatment can predict an even better response to treatment. Therefore, our results can be used to help guide clinical decision making.

Conclusion

In summary, prolactin normalization after 3 months of cabergoline treatment was a useful predictor of responsiveness in patients with prolactinoma. Moreover, a reduction in the prolactin level to ≤ 1 ng/mL after 3 months of cabergoline treatment predicted better response in patients with macroprolactinoma.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0753>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

D K was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education (NRF-2018R1D1A1B07050637). C R K was supported by the Bio and Medical Technology Development Program of the National Research Foundation (NRF) and funded by the Korean Government (MSIP and MOHW; No. NRF-2017M3A9E8029720).

Acknowledgement

The authors would like to thank Editage (www.editage.co.kr) for English language editing.

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Received 24 September 2019

Revised version received 13 November 2019

Accepted 26 November 2019