# Discrimination of prolactinoma from hyperprolactinemic non-functioning adenoma

Jae Won Hong

Department of Medicine

The Graduate School, Yonsei University

# Discrimination of prolactinoma from hyperprolactinemic non-functioning adenoma

Directed by Professor Eun Jig Lee

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Jae Won Hong

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This certifies that the Master's Thesis
of Jae Won Hong is approved.

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Thesis Supervisor : Eun Jig Lee

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Thesis Committee: Sun Ho Kim

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Thesis Committee: Young Soo Ann

The Graduate School
Yonsei University

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<ABSTRACT>

# Discrimination of prolactinoma from hyperprolactinemic non-functioning adenoma

Jae Won Hong

*Department of Medicine*
*The Graduate School, Yonsei University*

(Directed by Professor Eun Jig Lee)

The objective of this study was to evaluate characteristics that discriminate prolactinoma from non-functioning pituitary macroadenoma with hyperprolactinemia. We included 117 patients with hyperprolactinemic pituitary macroadenomas. Patients were divided into three groups according to treatment outcomes and pathologic results: (A) prolactinoma that responded to dopamine agonist (DA) treatment, PRDA; (B) prolactinoma requiring surgical treatment, PRS; and (C) non-functioning pituitary adenoma with hyperprolactinemia, NFPAH. Old age, low serum prolactin levels, and extrasellar extension were associated with NFPAH. Most patients with NFPAH had serum prolactin levels less than 100 ng/ml. Visual defects and GH deficiency were more common in patients with NFPAH compared with patients with PRS and PRDA, without difference of tumor size. Galactorrhoea and amenorrhoea were less frequent in patients with NFPAH than in patients with PRS and PRDA. Post-operative remission of hyperprolactinemia was achieved in 100% of patients with NFPAH and in 72.5% of patients with PRS. DA administration was required in 25.5% of patients with PRS; however, no patients with NFPAH required DA administration. In conclusion, old age, extrasellar tumor extension with

relatively low prolactin levels, visual defect and GH deficiency were considered suggestive of non-functioning pituitary adenoma rather than prolactinoma in hyperprolactinemic pituitary macroadenoma.

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Key words: prolactinoma, nonfunctioning pituitary adenoma, hyperprolactinemia

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Jae Won Hong

*Department of Medicine*
*The Graduate School, Yonsei University*

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## I. INTRODUCTION

Hyperprolactinemia is one of the most frequently diagnosed clinical disorders encountered in routine endocrine practice. It occurs in about 30% of women with galactorrhea or infertility and in 75% of women with amenorrhea and galactorrhea.[1] A prolactinoma diagnosis is most likely to be made when serum prolactin levels are greater than 200 ng/ml. However, when serum prolactin levels are lower than 200 ng/ml and above normal range, a differential diagnosis should be considered, including intake of various medications, polycystic ovarian syndrome, hypothyroidism, chronic renal failure, severe head trauma, and non-functioning pituitary adenoma (NFPA), which may also compress the pituitary stalk and cause hyperprolactinemia.[2] Taken together, hyperprolactinemia with the existence of pituitary adenoma is consistent with prolactinoma; however, it is not a clear diagnosis of prolactinoma.

Non-functioning pituitary microadenomas do not elevate serum prolactin levels. These small tumors associated with persistent hyperprolactinemia should be considered microprolactinomas and do not pose diagnostic difficulties. However, it is often difficult to discriminate prolactinoma from hyperprolactinemic NFPA, in particular in patients with pituitary macroadenoma. Most patients with

prolactinoma respond well to dopamine agonist (DA) therapy. DA therapy lowers serum prolactin levels and effectively reduces tumor size.[1-3] However, although serum prolactin levels can be lowered by DA treatment in patients with NFPAs, a reduction of tumor size is not achieved in the majority of patients.[4-6] When hyperprolactinemic pituitary macroadenoma with serum prolactin levels lower than 200 ng/ml is found, medical treatment can be first considered. NFPA or dopamine resistance is suspected when patients with hyperprolactinemic pituitary tumors do not respond to DA therapy.[7] These patients require surgery.[1, 6, 8] Determination of the timing of surgery is important because long-term use of DAs may cause fibrosis around the tumor, which makes tumor removal more difficult and increases the risk of adverse complications during the operative and post-operative periods, such as persistent hyperprolactinemia because of incomplete tumor excision and hypopituitarism because of damage to the normal gland.[9]

In this study, we evaluated the treatment outcomes of patients with hyperprolactinemic pituitary macroadenoma and analyzed the characteristics that discriminate NFPA accompanied by hyperprolactinemia from prolactinoma to build an appropriate therapeutic strategy for hyperprolactinemic pituitary tumors.

## II. MATERIALS AND METHODS

### Subjects and study design

This study included 117 patients with hyperprolactinemic (serum prolactin levels > 25 ng/ml) pituitary macroadenoma who were admitted to the Severance Hospital, Yonsei University, College of Medicine, Seoul, Korea, between 2005 and 2008. After excluding cases on the medications and on the presence of conditions capable of elevating the serum prolactin levels, magnetic resonance imaging (MRI) of the sella was performed. Each patient had a pituitary mass > 10 mm on MRI studies. Operations were performed on 70 patients by the same neurosurgeon (SH Kim) using the transsphenoidal approach (69) and craniotomy (1).

We retrospectively analyzed the medical records of patients involved in this study for the following information: age at diagnosis, sex, serum prolactin levels, symptoms at presentation, tumor size and extension by MRI, previous medical treatment and duration, reason for surgery, follow-up duration, post-operative medication, and pituitary functions evaluated by a cocktailed test.

Patients were divided into three groups according to treatment outcome and pathologic results as follows: (A) prolactinoma responding to DA treatment (PRDA), (B) prolactinoma requiring surgical treatment (PRS), and (C) NFPA with hyperprolactinemia (NFPAH). The PRS and NFPAH groups were diagnosed by immunohistochemical staining of surgically excised tumor tissues.

Surgery was recommended initially without DA use when a pituitary macroadenoma showed hemorrhage or cystic change on MRI, or was suspected to be an NFPA, including when hyperprolactinemia was present. Otherwise, once it was decided to administer a DA, bromocriptine was

started at a low dose in all patients (2.5 mg bromocriptine at bedtime) and the dose was gradually increased to 15 mg/day within a week. After two weeks, depending on serum prolactin levels, the dose was increased or maintained. The dosage was adjusted in a manner that allowed the maximum dose to be reached within one month. The maximum dose was determined by serum prolactin levels, symptom improvement, and side effects. Occasionally, before reaching the maximum dose of bromocriptine, patients complained of severe side effects or did not show lowered prolactin levels despite previous prolonged bromocriptine use, and bromocriptine was changed to cabergoline. At least three months after medication was begun, MRI examination and sampling of prolactin levels was performed to evaluate patient responsiveness to treatment. Then, we decided whether to continue medical treatment or to perform surgery. Surgery was recommended for patients who did not respond to bromocriptine or cabergoline. DA responsiveness requires the three following criteria: 1) normalization of serum prolactin levels; 2) shrinkage of the size of a tumor mass by more than 50%; and 3) no serious side effects. The study protocol was approved by the Institutional Review Board of Severance Hospital.

**Endocrinological evaluation**

Initial serum prolactin levels were obtained from Yonsei University College of Medicine or records of referring clinics. A cocktail test (regular insulin 0.15 unit/kg body weight, protirelin tartrate 500 mg, and gonadorelin 0.1 mg intravenously injected after baseline sampling with additional blood sampling at 15, 30, 60, 90, and 120 min) was initially performed to evaluate pituitary function during the preoperative period in most patients who underwent surgery. GH deficiency was determined by a peak GH level of < 3 ng/ml. ACTH deficiency, determined by measuring cortisol, was defined as peak cortisol level of < 180 ng/ml. TSH should increase by > 5 mU/l

unless thyroid hormone levels are increased. LH should increase by 10 IU/l and FSH by 2 IU/l. Remission of hyperprolactinemia was defined as post-operative normalization of serum prolactin levels (< 25 ng/ml) without DA treatment for at least two months.

**Prolactin assays**

The serum prolactin level was measured by Coat-A-Count Prolactin immunoradiometric assay (SIEMENS) (Conversion factor: ng/ml * 21.2 →m IU/L, within-run coefficient of variation: 1.1-2.7%, run-to-run coefficient of variation: 1.6-6.3%, reference range: males 3.1-16.5 ng/ml; females 3.6-18.9 ng/ml).

**Immunohistochemical staining**

Histopathological diagnoses were performed using hematoxylin–eosin staining and immunohistochemistry. Immunohistochemical studies for prolactin were performed using paraffin-embedded surgically excised pituitary adenomas. Pituitary sections of 4 μm were prepared. After deparaffinization and hydration of the slides, peroxidase quenching was performed with 3% hydrogen peroxide in PBS for 10 min. After pre-incubation with serum-blocking solution containing 10% rabbit serum, specimens were incubated with goat monoclonal anti-PRL antibody (Santa Cruz Biotechnology, Inc.) for 60 min at room temperature. After washing the slides with Tris-buffered saline/0.025% Tween, biotinylated rabbit anti-goat and streptavidin-peroxidase conjugate (Vector Laboratories, Inc.) were added sequentially. DAB (Vector Laboratories, Inc. Burlingame, CA) was used as a chromogen.

**Statistical analysis**

The data were expressed as the mean ± standard deviation. The statistical significance of differences in continuous variables was analyzed by Student's *t* test to make comparisons between the two groups and ANOVA for comparison between the three groups. Pearson's chi-squared test, linear by linear association, and Fisher's exact test were used for comparisons between categorical variables. Multiple logistic regression analysis was used to determine the variable associated with the post-operative remission. We entered in this analysis only those variables that had a *P* value less than 0.05 in the univariate analysis. A *P* value less than 0.05 was considered to be statistically significant. Statistical analyzes were performed using SPSS version 16.0.

## III. RESULTS

### Clinical characteristics of patients with hyperprolactinemic pituitary macroadenomas

A total of 117 patients with hyperprolactinemic pituitary macroadenomas were identified. The mean age at diagnosis was 35.4 ± 13.5 years. Thirty-one (26.5%) patients were male and 86 (73.5%) patients were female. Initial mean serum prolactin level was 330 ± 739.6 ng/ml (range, 25–5000 ng/ml). Based on MRI findings, all patients had macroadenomas. Fifty (42.7%) tumors were localized in the intrasellar area and 67 (57.3%) showed extrasellar extension. The mean tumor diameter was 24.2 ± 12 mm (Table 1).

**Table 1** Clinical characteristics of patients with hyperprolactinemic pituitary macroadenomas

| | Total (*n* = 117) | PRDA (*n* = 47) | PRS (*n* = 51) | NFPAH (*n* = 19) | *P*-value |
|---|---|---|---|---|---|
| **Sex, *n* (%)** | | | | | NS |
| Male | 31 (26.5) | 15 (31.9) | 14 (27.5) | 2 (10.5) | |
| Female | 86 (73.5) | 32 (68.1) | 37 (72.5) | 17 (89.5) | |
| **Age (years)*[a]** | 35.4 ± 13.5 | 34.1 ± 12.9 | 31.7 ± 11.5 | 46.6 ± 12.3 | < 0.0001 |
| **Serum prolactin levels (ng/ml)** | | | | | |
| Mean*[b] | 330 ± 739.6 | 504.5 ± 890.1 | 272.5 ± 691.9 | 52.7 ± 26.8 | < 0.0001 |
| Range**, *n* (%) | | | | | < 0.0001 |
| < 100 | 44 (37.6) | 5 (10.6) | 22 (43.1) | 17 (89.5) | |
| 100–200 | 22 (18.8) | 11 (23.4) | 9 (17.6) | 2 (10.5) | |
| > 200 | 51 (43.6) | 31 (66.0) | 20 (39.2) | 0 (0) | |
| **Extrasellar lesion**, *n* (%)** | | | | | 0.036 |
| Yes | 67 (57.3) | 23 (48.9) | 29 (56.9) | 15 (78.9) | |
| No | 50 (42.7) | 24 (51.1) | 22 (43.1) | 4 (21.1) | |
| **Tumor diameter , mm** | 24.2 ± 12.0 | 24.6 ± 14.5 | 22.0 ± 9.3 | 28.9 ± 10.5 | NS |
| **Hardy type, *n* (%)** | | | | | NS |
| I | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |
| II | 50 (42.7) | 24 (51.1) | 22 (43.1) | 4 (21.1) | |
| III | 37 (31.6) | 3 (6.4) | 23 (45.1) | 11 (57.9) | |
| IV | 30 (25.6) | 20 (42.6) | 6 (11.8) | 4 (21.1) | |

Data are expressed as mean ± standard deviation unless otherwise mentioned.

* Statistical significant by ANOVA

a. Post-hoc tests: The mean age was higher in the NFPAH group compared with the PRDA or PRS groups significantly by Scheffe procedure.

b. Post-hoc tests: The mean serum prolactin level (log transformed) in PRS was different from NFPAH or PRDA significantly by Scheffe procedure

** Statistical significant by $\chi^2$ *test*

DA (bromocriptine or cabergoline) was initially administered to 77 (65.8%) patients. Forty-seven (61%) of these 77 patients showed normalization of serum prolactin levels and reduced tumor sizes. Therefore, they continued to receive medical therapy (PRDA group). Surgical therapy was performed after DA use in 30 patients because of resistance (25 patients) or intolerance to DA (four patients). One remaining patient received bromocriptine for one month and showed lowered prolactin levels (283 ng/ml to 42.9 ng/ml). However, he subsequently developed pituitary apoplexy and underwent surgery.

Among 25 patients who did not respond to DA treatment, 12 patients did not undergo normalization of serum prolactin levels or tumor size reduction. Ten patients achieved normalization of serum prolactin levels and did not show tumor size reduction by 25%. The remaining three patients showed a mass reduction of more than 25%; however, serum prolactin levels in these patients did not drop to within the normal range. In these 25 DA-resistant patients, the mean duration of DA use before surgery was 7.6 ± 8.7 months. The maximum dose of bromocriptine was 15–20 mg/day, and the maximum dose of cabergoline was 1–2 mg/week.

Forty patients (34.2%) had never received DAs and were treated surgically first because they showed various NFPA characteristics (35 patients), and hemorrhage or cystic change (five patients) in the tumor on MRI, even when hyperprolactinemia was present. We performed immunohistochemical staining for prolactin in all surgically excised tumor tissues. Fifty-one tumors were positive for prolactin and classified as prolactinomas requiring surgery (PRS

group). Tumors from 19 patients showed negative results for prolactin immunohistochemical staining and were classified as NFPA with hyperprolactinemia (NFPAH group) (Fig. 1, Table 2).

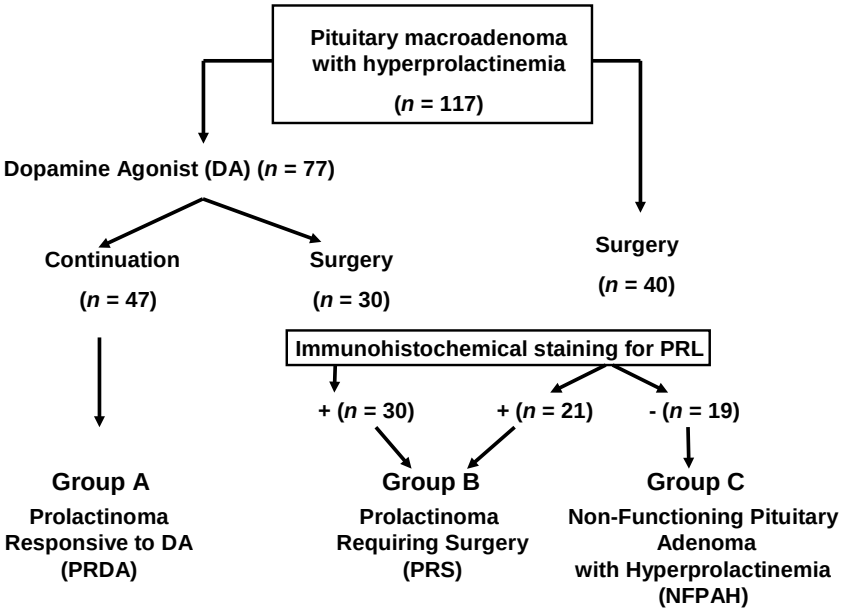


**Figure 1. Classification of hyperprolactinemic pituitary tumuors according to treatment and pathologic results.**

**Table 2** Reasons for surgery in patients with hyperprolactinemic pituitary macroadenoma

| *n* (%) | Total (*n* = 70) | PRL (+) (*n* = 51) | PRL (–) (*n* = 19) |
|---|---|---|---|
| Drug resistance | 25 (35.7) | 25 | 0 |
| Drug intolerance | 4 (5.7) | 4 | 0 |
| Hemorrhage/cystic change | 5 (7.1) | 4 | 1 |
| Suspicious NFPA | 35 (50.0) | 17 | 18 |
| Tumor apoplexy | 1 (1.4) | 1 | 0 |

The sex ratio was not different between the groups. The mean age (46.6 ± 12.3 years) was higher in the NFPAH group compared with the PRDA (34.1 ± 12.9 years) and PRS (31.7 ± 11.5 years) groups ($P < 0.0001$).

The majority of patients in the PRDA group (89.4%) had initial serum prolactin levels higher than 100 ng/ml. About 66% of patients in the PRDA group had serum prolactin levels higher than 200 ng/ml. Most patients (89.5%) with NFPAH had serum prolactin levels less than 100 ng/ml and only 10% of patients with NFPAH had serum prolactin levels above 100 ng/ml; no patients with NFPAH had serum prolactin levels higher than 200 ng/ml (Fig. 2). Patients in the PRDA group had significantly higher prolactin levels (log transformed) than patients in the PRS or NFPAH groups ($P < 0.0001$). The tumor size was not different among the three groups. Univariate analysis revealed that lower prolactin levels (log transformed), extrasellar extension, and older age were associated with NFPAH (Table 1).

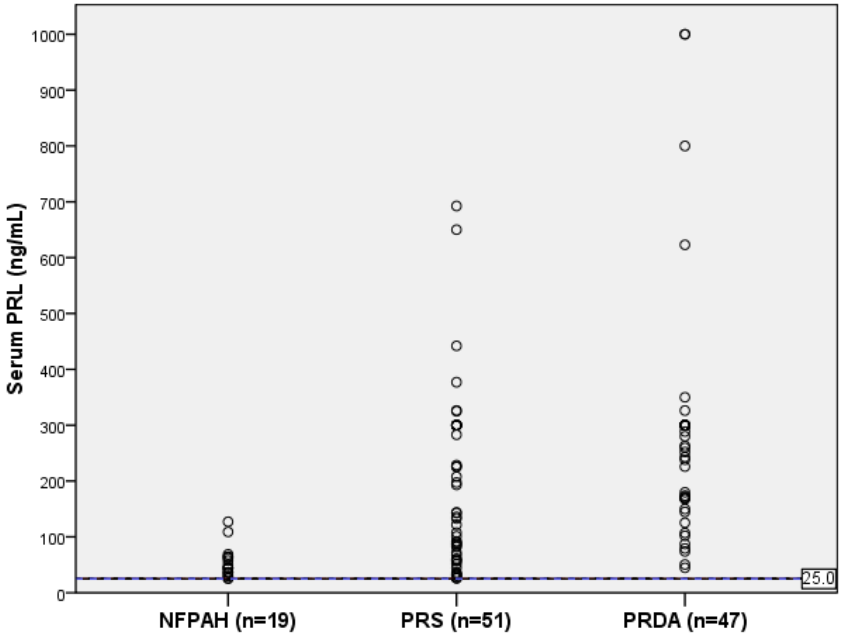

**Figure 2. Range of serum prolactin levels in patients with NAPAH, PRS and PRDA.** Most patients with NFPAH had serum prolactin levels less than 100 ng/ml and no patients with NFPAH had serum prolactin levels higher than 200 ng/ml. On the contrary, the majority of patients in the PRDA group had initial serum prolactin levels higher than 100 ng/ml.

**Presenting manifestations of patients with hyperprolactinemic pituitary tumor**

Amenorrhea and/or infertility were observed in 58 (49.6%) of 117 patients with pituitary macroadenomas. These symptoms were predominantly observed in patients in the PRDA (53.2%) and PRS (58.8%) groups; however, 15.8% of patients with NFPAH complained of amenorrhea and/or infertility. Visual defects were the second most frequently noted clinical manifestation and were observed in 42 patients (35.9%). Visual defects were more common in patients in the NFPAH group (73.7%) than in patients in the PRS (35.3%) and PRDA (21.3%) groups ($P < 0.001$, Table 3).

**Table 3** Presenting manifestations of patients with hyperprolactinemic pituitary tumor

| *n* (%) | Total (*n* = 117) | PRDA (*n* = 47) | PRS (*n* = 51) | NFPAH (*n* = 19) | *P*-value |
|---|---|---|---|---|---|
| Amenorrhea, infertility * | 58 (49.6) | 25 (53.2) | 30 (58.8) | 3 (15.8) | 0.036 |
| Visual defect * | 42 (35.9) | 10 (21.3) | 18 (35.3) | 14 (73.7) | < 0.0001 |
| Galactorrhea * | 13 (11.1) | 8 (17.0) | 5 (9.8) | 0 (0) | 0.04 |
| Headache, dizziness | 15 (12.8) | 6 (12.8) | 4 (7.8) | 5 (26.3) | NS |
| Sexual dysfunction | 8 (6.8) | 5 (10.6) | 3 (5.9) | 0 (0) | NS |
| Incidental finding | 5 (4.3) | 4 (8.5) | 0 (0) | 1 (5.3) | NS |
| Hair loss, delayed puberty | 4 (3.4) | 3 (6.4) | 1 (2) | 0 (0) | NS |

* Statistical significant by $\chi^2$ *test*

**Preoperative pituitary function in patients with PRS and NFPAH**

Preoperative combined pituitary function tests were performed in 66 patients. We observed GH deficiency (51.5%), LH deficiency (45.5%), TSH deficiency (27.3%), ACTH deficiency (18.4%), and FSH deficiency (18.2%). GH deficiency was more common in patients with NFPAH compared with patients with PRS (P = 0.013; Table 3). Patients in the NFPAH group had a higher frequency of any pituitary hormone deficiency (88.9%) compared with patients in the PRS group (60.4%) (P = 0.037; Table 4).

**Table 4** Preoperative pituitary function of patients with PRS or NFPAH

| Deficient hormone *n* (%) | Total *n* = 66 | PRS *n* = 48 | NFPAH *n* = 18 | *P*-value |
|---|---|---|---|---|
| GH* | 34 (51.5) | 20 (41.7) | 14 (77.8) | 0.013 |
| TSH | 18 (27.3) | 12 (25.0) | 6 (33.3) | NS |
| FSH | 12 (18.2) | 10 (20.8) | 2 (11.1) | NS |
| LH | 30 (45.5) | 19 (39.6) | 11 (61.1) | NS |
| ACTH | 14 (18.4) | 10 (17.2) | 4 (22.2) | NS |
| Number of hormone deficiencies | | | | |
| 0* | 21 (31.8) | 19 (39.6) | 2 (11.1) | 0.037 |
| 1 | 11 (16.7) | 8 (16.7) | 3 (16.7) | NS |
| 2 | 15 (22.7) | 7 (14.6) | 8 (44.4) | NS |
| ≥ 3 | 19 (28.8) | 14 (29.2) | 5 (27.8) | NS |

* Statistical significant by *Fisher's exact test*

**Surgical outcome of patients with PRS and NFPAH**

We performed surgery on 70 patients (51 from the PRS group and 19 from the NFPAH group) using transsphenoidal (69 patients) and transfrontal approaches (one patient). Total resection of the pituitary tumor was performed in 61 (87.1%) patients, which was confirmed by post-operative MRI examination. The remaining nine (12.9%) patients underwent subtotal resection of pituitary tumors because most of them (eight patients) had cavernous sinus invasion. The remaining patient who underwent subtotal resection had a suprasellar pituitary

adenoma that had severe adhesion to the superior area of the tumor mass. In this patient, removing the entire tumor mass including the fibrotic capsule might have caused optic nerve injury.

Post-operative remission of hyperprolactinemia was achieved in the 19 patients with NFPAH. No patient with NFPAH required post-operative DA treatment (Table 5). Among the 51 patients with PRS, normalization of serum prolactin levels was not achieved in 14 (27.5%) patients (five patients with subtotally resected tumors and nine of 56 patients with totally resected tumors) who required additional DA therapy post-operatively. Univariate analysis revealed that higher prolactin levels at post-operative day 7, higher prolactin levels at diagnosis (log transformed), larger tumor size, previous use of DAs, and subtotal resection of tumors were associated with non-remission of hyperprolactinemia. However, age at diagnosis, sex, and extrasellar extension were not associated with remission of hyperprolactinemia.

**Table 5** Surgical outcomes of patients with PRS and NFPAH

| | Total ($n$ = 70) | PRS ($n$ = 51) | NFPAH ($n$ = 19) | $P$-value |
|---|---|---|---|---|
| **Resection, *n* (%)** | | | | NS |
| Total | 61 (87.1) | 46 (90.2) | 15 (78.9) | |
| Subtotal | 9 (12.9) | 5 (9.8) | 4 (21.1) | |
| Cavernous sinus invasion | 8/9 (89) | 4/5 (80) | 4/4 (100) | |
| **Serum prolactin levels at post-operative day 7 (ng/ml)** | | | | NS |
| Mean | 21.33 ± 49.99 | 25.07 ± 58.08 | 11.25 ± 7.86 | |
| Range, *n* (%) | | | | |
| < 25 | 57 (81.4) | 39 (76.5) | 18 (94.7) | |
| 25–50 | 10 (14.3) | 9 (7.6) | 1 (5.3) | |
| 50–100 | 1 (1.4) | 1 (2) | 0 (0) | |
| > 100 | 2 (2.9) | 2 (3.9) | 0 (0) | |
| **Normalization of serum prolactin levels*, *n* (%) by surgery alone** | | | | 0.008 |
| Yes | 56 (80) | 37 (72.5) | 19 (100) | |
| No | 14 (20) | 14 (27.5) | 0 (0) | |
| **Post-operative DA medication*, *n* (%)** | | | | 0.014 |
| Yes | 13 (8.6) | 13 (25.5) | 0 (0) | |
| No | 57 (81.4) | 38 (74.5) | 19 (100) | |

| | | | | |
|---|---|---|---|---|
| **Recurrence of hyperprolactinemia, *n* (%)** | | | | NS |
| Yes | 4 (5.7) | 4 (7.8) | 0 (0) | |
| No | 66 (94.3) | 47 (92.2) | 19 (100) | |

Data are expressed as mean ± standard deviation unless otherwise mentioned.

* Statistical significant by *Fisher's exact test*

In a multiple logistic regression analysis, we included age, sex, tumor size, preoperative prolactin levels (log transformed), prolactin levels at post-operative day 7, and total resection. Among 25 patients in the PRS group who underwent surgical treatment because of DA resistance, 13 (52%) patients achieved surgical cures. However, eight (32%) patients required post-operative DA treatment for normalization of hyperprolactinemia, and the remaining four (16%) patients had persistently elevated prolactin levels despite post-operative DA treatment.

The recurrence of pituitary masses or hyperprolactinemia among patients who only received surgical treatment occurred in the PRS group and not the NFPAH group. Among the 51 patients in the PRS group, recurrent pituitary masses occurred in two patients, who also had recurrence of hyperprolactinemia. The recurrence of hyperprolactinemia occurred in four patients in the PRS group, including the two patients who had recurrent pituitary masses.

## IV. DISCUSSION

Prolactinoma is the most common pituitary adenoma and accounts for up to 45% of pituitary tumors.[10] The first treatment of choice for prolactinoma is DA therapy with bromocriptine or cabergoline, which is effective in reducing the size of tumors and normalizing prolactin levels.[1] NFPA constitutes about 25% to 35% of pituitary tumors. Concomitant hyperprolactinemia was encountered in approximately 20-30 % of patients with NFPA. [11, 12] Although DAs, GnRH antagonists, and somatostatin analogues modestly shrink tumors in a select population of patients, they are not sufficiently effective to be recommended as a therapy and surgical therapy should be considered. [4]

It is sometimes difficult to distinguish prolactinoma from NFPAH, especially in patients with macroadenoma. Most patients with NFPAs have macroadenomas and the main presenting symptoms are visual defects and headache.[13] However, to our knowledge, there have been few reports that have compared the clinical characteristics of prolactinoma and NFPAH between two groups without mass effect, excluding microprolactinoma. We included pituitary macroadenoma, and intrasellar and extrasellar lesions because non-functioning pituitary macroadenoma within the sellar can also develop into mild hyperprolactinemia by elevation of intrasellar pressure, as well as NFPA with suprasellar extension causing stalk compression.[14]

In this study, patients with NFPAH tended to be older (46.6 ± 12.3 years) compared with patients with PRS or PRDA. Ferrante *et al*. reported that the mean age of 295 patients with NFPAs registered in seven Endocrinological Centers of North West Italy was 50.4 ± 14.1 years (range 14-78 years).[12] However, the development of NFPA compared with that of prolactinoma may not occur exclusively in older patients. We only included patients who had been surgically treated for non-functioning pituitary tumors with serum prolactin

levels above 25 ng/ml, which represented large tumors that compressed the pituitary stalk. Delayed diagnosis because of hormonal inactivity is a cause of the higher incidence of NFPAH compared with that of prolactinoma in older patients. In the clinic, the possibility of NFPA should be considered, especially when patients are older than 40 years of age with pituitary masses and mild hyperprolactinemia.

When serum prolactin levels were divided into three groups, with levels of < 100 ng/ml, 100–200 ng/ml, or > 200 ng/ml, patients with NFPAH had lower serum prolactin levels than patients with PRS and PRDA ($P < 0.001$). Furthermore, among patients with NFPAH, the highest prolactin level was 127 ng/ml. Wass *et al*. reported that serum prolactin levels > 100 ng/ml (2000 mU/l) are almost never encountered in patients with non-functioning pituitary macroadenomas.[15] Buchfelder *et al*. reported that hyperprolactinemia occurred in 19% (167 out of 882 patients) of patients with NFPAs and serum prolactin levels at presentation did not exceed 157 ng/ml (3150 mU/l).[11]

In this study, 17 of 35 patients who underwent surgery because of suspected NFPA had prolactinomas that were prolactin-positive. Interestingly, the prolactin levels in these patients were relatively low (< 150 ng/ml) despite larger tumor sizes and exclusion of the hook effect by measuring serum prolactin by dilution. This suggests that secretory activity may differ according to prolactinoma subtype. Therefore, DAs should be considered before surgery, even when a patient is suspected to have NFPA. However, if these patients do not respond to DAs within three months, especially in tumor size reduction, surgery should not be delayed because prolonged use of DAs may cause peritumoral fibrosis and make tumor resection difficult. Furthermore, most tumor shrinkage occurs during the first three months of treatment.[16-19]

Visual defects were more common in patients with NFPAH compared with patients with PRS and PRDA. GH deficiency was also more common in

patients with NFPAH. These findings were considered to be caused by the mass effect of the pituitary tumor. In previous studies, the prevalence of visual defects in patients with NFPA was reported to be 30% to 68%. [4, 12, 13, 20, 21] In our study, a higher frequency of visual defects was reported in patients with NFPAH (73.7%) because this study only included surgically treated NFPAs. In general, if NFPA threatens vision or a macroadenoma is large enough to threaten vital structures, transsphenoidal surgery is recommended.[2] At our hospital, suprasellar masses, which may compress the optic nerve, and macroadenoma with internal hemorrhage, were indications for surgery.

In numerous previous studies, lower preoperative prolactin levels and smaller tumor size have been used as predictive factors for remission.[22-26] However, the only predictive factor for hyperprolactinemia remission in this study was prolactin levels at post-operative day 7. Surgical outcome may be predicted by checking prolactin levels at post-operative day 7 as well as preoperative prolactin levels.

We suggest that old age, extrasellar tumor extension with relatively low prolactin levels, visual defect and GH deficiency were considered suggestive of NFPA rather than prolactinoma in hyperprolactinemic pituitary macroadenoma. Most patients with NFPA had serum prolactin levels less than 100 ng/ml. Post-operative remission of hyperprolactinemia without DA administration was achieved in 100% of patients with NFPA

## V. CONCLUSION

In conclusion, old age, extrasellar tumor extension with relatively low prolactin levels, visual defect and GH deficiency were considered suggestive of non-functioning pituitary adenoma rather than prolactinoma in hyperprolactinemic pituitary macroadenoma.

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< ABSTRACT (IN KOREAN)>

# 고프로락틴혈증을 동반한 비기능성 뇌하수체 종양과 프로락틴 분비 선종의 구분

<지도교수 이은직>

연세대학교 대학원 의학과

홍재원

이 연구의 목적은 고프로락틴혈증을 동반한 비기능성 뇌하수체 종양과 프로락틴 분비 선종을 구분할 수 있는 특징을 밝히는 것이다. 고프로락틴혈증이 있고 뇌하수체 거대선종을 가진 117 명의 환자를 치료 결과와 병리학적 진단에 따라서 다음과 같이 세 군으로 분류하였다. (A) 도파민 작용제에 효과가 있는 프로락틴 분비 선종, PRDA; (B) 수술적 치료가 필요한 프로락틴 분비 선종, PRS; 그리고 (C) 고프로락틴혈증을 동반한 비기능성 뇌하수체 선종, NFPAH.

고프로락틴혈증을 동반한 비기능성 뇌하수체 선종환자는 프로락틴 분비 선종에 비해서 나이가 많고, 혈중 프로락틴 수치가 낮았으며, 터어키안 외부로 확장 하는 경향이 있었으며 대부분의 환자에서 혈중 프로락틴 수치가 100 ng/ml 이하였다. 종양의 크기는 차이가 없음에도 불구하고, 시야 장애와 성장호르몬 부족도 프로락틴 분비 선종에 비해 비기능성 뇌하수체 선종에서 더 흔하게 나타났다. 유즙분비와 무월경은 프로락틴 분비 선종에 비해서 비기능성 뇌하수체 선종환자에서 더 드물게 발생했다. 수술 후 고프로락틴혈증의 관해는 비기능성 뇌하수체 선종환자에서는 100% 에서 이루어졌지만, 프로락틴 분비

선종 환자에서는 72.5% 에서 이루어졌다. 또한 수술 후 프로락틴 분비 선종 환자에서는 25.5% 에서 도파민 작용제 투여가 필요했으나, 비기능성 뇌하수체 선종 환자에서 도파민 작용제 투여가 필요한 경우는 없었다. 결론적으로, 고프로락틴혈증을 동반한 뇌하수체 거대선종을 가진 환자에서 나이가 많고, 낮은 혈중 프로락틴 수치, 터어키안 외부로의 확장, 시야 장애, 성장 호르몬 감소를 동반한 경우, 프로락틴 분비 선종보다는 비기능성 뇌하수체 선종의 가능성을 고려해야 하겠다.

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핵심되는 말: 프로락틴 분비 선종, 비기능성 뇌하수체 선종, 고프로락틴혈증