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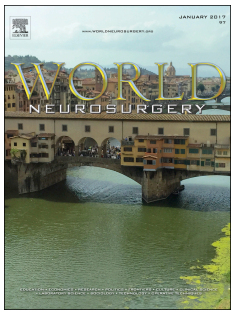

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PII: S1878-8750(18)31851-5

DOI: 10.1016/j.wneu.2018.08.068

Reference: WNEU 8926

To appear in: *World Neurosurgery*

Received Date: 1 May 2018

Revised Date: 10 August 2018

Accepted Date: 11 August 2018

Please cite this article as: Park SS, Kim JH, Kim YH, Lee JH, Dho Y-S, Shin CS, Clinical and radiographic characteristics related to hyperprolactinemia in nonfunctioning pituitary adenomas, *World Neurosurgery* (2018), doi: 10.1016/j.wneu.2018.08.068.

Clinical and radiographic characteristics related to hyperprolactinemia in nonfunctioning pituitary adenomas

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Keywords: Nonfunctioning pituitary adenoma, stalk effect, hyperprolactinemia, hypopituitarism

Abbreviation List :

ACTH : adrenocorticotropic hormone

AP : anteroposterior

BMI : body mass index

E2 : estradiol

FSH : follicular stimulating hormone

GH : growth hormone

GKS : gamma knife surgery

IGF-1 : insulin-like growth factor 1

IRMA : immunoradiometric assay

LH : luteinizing hormone

MRI : magnetic resonance imaging

NFPAs : non-functioning pituitary adenomas

RIA : radioimmunoassay

T4 : free thyroxine

TSA : transsphenoidal surgery

TSH : thyroid-stimulating hormone

Abstract

Objective

Hyperprolactinemia in non-functioning pituitary adenomas (NFPAs) subjects has been explained by the stalk compression of "large" pituitary adenomas. However, not all "large" NFPAs present high serum prolactin levels. Thus, we aimed to elucidate and compare clinical, hormonal, and radiographic characteristics of NFPAs with and without hyperprolactinemia.

Methods

We included 201 subjects with clinically NFPAs who underwent transsphenoidal surgery by a single surgeon during 2010–2017 at a single center in Korea. We measured the three-dimensional diameters (anteroposterior [AP], width, height) and volumes of NFPA on magnetic resonance imaging. We conducted the morning basal hormone measurement and dynamic tests preoperatively and at 3 months postoperatively.

Results

All NFPAs were macroadenomas, and the mean tumor volume was 10.4 ± 7.7 cm^3. Of 201 subjects, 59 (29.4%) had preoperative hyperprolactinemia. Hormone recovery rate was higher in subjects with hyperprolactinemia than in those without hyperprolactinemia after age, sex, body mass index, tumor volume, and gross total resection adjustments (odds ratio [95% confidence interval]: 2.55 [1.10–5.92]). Tumor width per AP diameter ratio positively correlated with serum prolactin levels (r = 0.186, P = 0.008). However, tumor volume was not significantly different between two groups.

Conclusions

Preoperative prolactin level is a useful marker to predict hormone recovery after surgery. NFPA subjects with hyperprolactinemia tended to have a higher width per AP diameter ratio and hyperprolactinemia of NFPA is more likely affected by tumor growth pattern such as width/AP diameter than tumor volume itself.

Introduction

Nonfunctioning pituitary adenomas (NFPAs) are most common among pituitary adenoma subtypes. Patients with NFPAs mainly presented mass effects such as visual field defects or headaches, but some of them, *i.e.*, premenopausal women, complained of galactorrhea or amenorrhea due to hyperprolactinemia. The prevalence of hyperprolactinemia in NFPAs is around 25%–65% with a mean level of 39 ng/mL, as estimated in recent meta-analyses [1, 2].

The putative mechanism is that the mechanical compression of the pituitary stalk by NFPAs reduces dopamine signaling to lactotroph cells, disinhibiting the physiological suppression of prolactin secretion by dopamine [3-8]. However, all large NFPAs (maximal diameter ≥ 1cm) did not show hyperprolactinemia [9]. Even giant pituitary adenomas can expand into the cavernous sinus or suprasellar area without compressing the pituitary stalk. Conversely, small microadenomas also elevate prolactin level by disturbing the portal flow [10]. The weak relationship between serum prolactin level and tumor size was partially explained by increased intrasellar pressure [11]. Increased intrasellar pressure was also associated with hypopituitarism as well as hyperprolactinemia, thereby disturbing the hypothalamic-pituitary releasing hormone and functions of the normal anterior pituitary gland [11].

We hypothesize that the growing pattern of NFPAs, estimated by three-dimensional size measurement, affects serum prolactin level and the relatively "large-volume" tumor may lose the characteristics of hyperprolactinemia and subsequently progress into irreversible pituitary gland failure, including lactotroph cells failure. Here, we aimed to elucidate and compare the features of NFPAs with and without hyperprolactinemia in terms of clinical, hormonal, and radiographic characteristics.

Material and Methods

Study subjects

We screened 374 subjects and included 201 subjects (102 male, 99 female) who were diagnosed with clinically NFPAs and underwent endoscopic transsphenoidal surgery(TSA) owing to visual field defects at Seoul National University Hospital in Korea between March 2010 and October 2017. The same surgeon (Y.H.K) performed surgery in all subjects. We excluded possible prolactinoma on the basis of preoperative prolactin level of >200 ng/mL [1, 12]. Serum samples of subjects with prolactin level > 25 ng/mL were sequentially diluted and retested to identify the hook effect. Among subjects of clinically NFPA, 108 subjects with previous TSA or gamma knife surgery (GKS) were excluded. A total of 62 subjects were excluded due to the presence of positive immunohistochemical staining for prolactin. Three patients did not present visual field defects but underwent TSA due to rapidly growing pituitary adenomas. In final analysis, we included 201 patients who underwent surgery for visual field defects with suprasellar extension (**Figure 1**). All study subjects were followed up at 3 months after surgery to assess postoperative hormone status and complications. The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB no. 1503-040-654).

Magnetic resonance imaging (MRI) assessment

Magnetic resonance imaging (MRI) of the sellar area was performed in all patients. A 1.5- or 3-Tesla MRI with T1- and T2-weighted spin echo technique without and with gadolinium-based contrast medium was used. Three-dimensional diameter (anteroposterior [AP], width, height) and volume of NFPAs were obtained using MRI. The volume of the tumor was calculated by multiplying the tumor area measurement with contour lines of each coronal view and the slice thickness. In order to reduce measurement errors, the volume was measured twice and the mean value was used. The presence of cavernous sinus invasion was also assessed using MRI.

The degree of tumor resection was determined according to both the surgeons' intraoperative vision and postoperative MRI findings. Gross total resection indicated that the tumor was totally removed based on the surgeon's view, and there was no residual tumor detected on immediate postoperative MRI. The coronal T1-weighted contrast imaging was used to detect cavernous sinus invasion according to the Knosp classification [13], in which grades 3 and 4 indicated a cavernous sinus invasion.

Hormone assessment

Morning basal hormone measurement and dynamic hormone tests were performed to assess the hormone

deficiency preoperatively and at 3 months after surgery. We measured the levels of growth hormone (GH), insulin-like growth factor 1 (IGF1), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2) or total testosterone, free thyroxine (T4), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH),serum cortisol, and serum prolactin in all patients preoperatively and at 3 months after surgery. All hormone measurements were performed between 8 am and 10 am, and all hormones were measured using radioimmunoassay (RIA) or immunoradiometric assay (IRMA).

Hyperprolactinemia was defined when serum prolactin level was over 20 ng/mL in men and over 25 ng/mL in women. Serum samples with prolactin level> 25 ng/mL were retested with sequentially diluted sample to assess the hook effect. GH deficiency was defined according to the results of insulin-induced hypoglycemia test (peak GH level < 3 μg/L). In the absence of insulin-induced hypoglycemia test results, GH deficiency was defined as a condition in which IGF1 was below the normal level and all three other hormones (ACTH, TSH, and gonadotropin) were deficient. ACTH deficiency was defined based on the result of a short Synacthen® (tetracosactide) test or an insulin-induced hypoglycemia test (peak cortisol < 18 μg/dL). When these tests were not performed, ACTH deficiency was defined as low morning cortisol levels and below normal ACTH levels. TSH deficiency was defined as low free T4 (<0.70 ng/dL) level under low-normal TSH level (≤ 4.1 μIU/mL). Gonadotropin deficiency was defined when premenopausal women showed amenorrhea or FSH level was <30 mIU/ml in postmenopausal women. In men, gonadotropin deficiency was defined as testosterone levels below normal (<2.8 ng/mL) under low-normal FSH/LH level. Central diabetes insipidus was diagnosed if patients presented with water diuresis and polydipsia and responded to desmopressin.

Statistical analysis

For continuous variables, student *t*-test or Mann–Whitney *U* test were used to compare between subjects with and without hyperprolactinemia. The skewed variables, such as serum prolactin level, tumor volume, and tumor three-dimensional diameters were log-transformed. For categorical variables, the difference was analyzed using the chi-square test or Fisher's exact test. The correlation between tumor width/AP diameter ratio calculated using MRI and serum prolactin level was assessed using Pearson's correlation analysis. The effects of preoperative prolactin level, age, sex, body mass index (BMI), tumor volume, and gross total resection on hormone recovery were analyzed using multivariate logistic regression models. *P* value of <0.05 was considered to be statistically significant and all statistical analyses were performed using SPSS software (version 24; SPSS

Inc., Chicago, IL).

Results

Baseline characteristics of study subjects (n = 201; male, 101 [50.7%]) were described in **Table 1**. The mean age was 51.1 years and the mean BMI was 25.5 kg/m^2. The mean tumor AP diameter, height, and width assessed using MRI were 22.6 ± 7.0 mm, 30.3 ± 7.7 mm, and 26.8 ± 6.3 mm, respectively. The mean tumor volume calculated using MRI was 10.4 ± 7.7 cm^3. Cavernous sinus invasion was confirmed in 49.0% (n = 98) of the study subjects. Preoperative GH, ACTH, TSH, and gonadotropin deficiencies were observed in 40.2%, 29.0%, 18.7%, and 61.2% of the study subjects. There were 132 (68.4%) subjects deficient in any one of the hormones, and 24 (12.4%) subjects deficient in all hormones, except GH, preoperatively.

We compared clinical and hormonal characteristics between the clinically NFPA subjects with and without hyperprolactinemia (**Table 2**). Among 201 subjects, 59 (29.4%) subjects exhibited hyperprolactinemia. The proportion of women in subjects with hyperprolactinemia was higher than that without hyperprolactinemia. Subjects with hyperprolactinemia were younger than those without hyperprolactinemia. The prevalence of preoperative TSH, and gonadotropin deficiency was higher in subjects with preoperative hyperprolactinemia than in those without hyperprolactinemia. Postoperative hyperprolactinemia newly occurred in 1 subjects (0.7%) without preoperative hyperprolactinemia and was sustained in 4 subjects (6.9%) with preoperative hyperprolactinemia. Hyperprolactinemia did not affect the development of postoperative diabetes insipidus.

In addition, we performed logistic regression model analysis to elucidate whether preoperative serum prolactin level predicts hormone recovery in subjects with preoperative ACTH or TSH deficiency (n = 135) (**Table 3**). Compared with subjects without hyperprolactinemia, hormone recovery rate was higher in those with hyperprolactinemia even after adjustments were made for age, sex, BMI, tumor volume, and gross total resection (odds ratio [95% confidence interval, CI], 2.55 [1.10–5.92]).

Radiographic characteristics of NFPAs with hyperprolactinemia were also analyzed in **Table 4**. Tumor volume was not significantly different between subjects with and without preoperative hyperprolactinemia (9.6 ± 7.5 cm^3, 10.7 ± 7.8 cm^3 respectively, *P= 0.365*). Tumor AP diameter, height, width and cavernous sinus invasion were also not significantly different between two groups. NFPAs with hyperprolactinemia had significantly higher ratios of tumor width per AP dimeter than those without hyperprolactinemia, although the ratio of tumor height per width diameter was not different between groups. The scatter plot between serum prolactin level and

tumor width per AP diameter ratio was shown in **Figure 2**. Tumor width per AP diameter ratio was positively related with serum prolactin levels ($r = -0.163$, $P = 0.021$)

Discussion

In the present study, 59 (29.4%) of 201 NFPA subjects preoperatively exhibited hyperprolactinemia. Hyperprolactinemia in NFPAs was associated with young age, being female. Subjects with preoperative hyperprolactinemia revealed higher odds of postoperative hormone recovery than those without hyperprolactinemia after adjustment were made for age, sex, tumor volume, BMI, and gross total resection. Tumor volumes were not significantly different between subjects with hyperprolactinemia and those without. However, higher ratio of tumor width per AP diameter was observed in NFPAs with hyperprolactinemia than in those without hyperprolactinemia.

NFPA subjects with hyperprolactinemia were mostly young and female. Most young females experienced galactorrhea or amenorrhea as a symptom of hyperprolactinemia, but postmenopausal women as well as men didn't present that symptoms. They even overlooked a symptom of hyperprolactinemia such as decreased libido. This is the reason for hyperprolactinemia in NFPAs being a common phenomenon in young females similar to female preponderance of microprolactinomas. A similar observation was reported in another study [12].

The stalk effect may affect other pituitary hormones other than prolactin, inhibiting releasing factors from the hypothalamus to the pituitary gland. In this perspective, hyperprolactinemia may be related with hypopituitarism. On the other hand, relatively large NFPAs with normal prolactin levels may elevate intrasellar pressure and disturb the blood flow or injure the pituitary gland, leading to pituitary hormone insufficiency [11]. Bergsneider et al. also postulated that the state of normoprolactinemia is more progressive than the state of hyperprolactinemia, in which other pituitary hormone-secreting cells also fall into a state of atrophy [12]. However, in the present study, TSH and gonadotropin deficiency was more prevalent in subjects with hyperprolactinemia than those without hyperprolactinemia. Nonetheless, preoperative hyperprolactinemia was a considerably good predictor of postoperative hormone recovery. Another study has also shown similar results [14]. In hyperprolactinemia, lactotroph cells may be intact and reactive to the disinhibition of inhibitory signaling as opposed to normoprolactinemia. At the early pituitary adenoma development stage, hyperprolactinemia occurs as a pituitary stalk compression, but as pituitary adenoma grows, the compression becomes worse and inhibits the releasing hormone from the hypothalamus, leading to irreversible pituitary gland atrophy. Accordingly, serum prolactin levels fall sequentially from a high to low level. In other words, the degree of serum prolactin level may be inversely proportional to the severity of pituitary damage, which support the results of our study, *i.e.*, hormone

recovery is good in subjects with hyperprolactinemia than those without hyperprolactinemia.

Based on the stalk effect theory, it is natural that NFPAs with hyperprolactinemia are accompanied with a large tumor size, as suggested by Zaidi et al. [15]. However, we demonstrated that maximal tumor diameter or tumor volume were not different between subjects with and without hyperprolactinemia, like that observed in other studies [8, 9]. Zaidi et al. included all patients with sellar lesions, such as functioning microadenomas and other sellar mass, and measured only the maximal axial tumor diameter [15]. In the present study, we included subjects with only clinically nonfunctioning pituitary macroadenomas, who needed surgical removal, and evaluated the AP diameter, height, width, and tumor volumes using MRI to assess the growth pattern. The mean maximal tumor diameter in our study was approximately 30.9 mm, which was larger than that reported in the study by Zaidi et al. [15]. On the contrary, Bergsneider et al. proposed that the hyperprolactinemia phase by stalk effect precedes the normoprolactinemic status in NFPAs [12]. Lactotroph disinhibition may be followed by lactotroph failure due to decreased unknown stimulating factors or direct damage of normal lactotroph by macroadenomas. The stalk effect can be observed even in subjects with normal prolactin levels. After surgery, preoperative serum prolactin level decreased significantly even in subjects with preoperative normoprolactinemia (9.6 ± 5.5 vs. 5.7 ± 3.7, $P < 0.001$), similar to previous studies [12, 16]. Accordingly, the stalk effect may be transient in the progression of “small” macroadenomas to “large” macroadenomas. However, the relationship between tumor volume and serum prolactin level was not significant in the present study. Intriguingly, the higher ratio of width per AP diameter was shown in NFPAs with hyperprolactinemia. A previous study showed that the average AP diameter of sella turcica was 8 mm and the average width was 12 mm.[17] The putative mechanism is that NFPAs can increase the intrasellar pressure more rapidly when they grow anteroposteriorly rather than laterally, because the AP diameter of the sella is shorter than its width. This leads to low prolactin level and pituitary insufficiency.

It has been shown that decompressing the stalk by surgical removal of NFPAs can normalize the stalk effect-induced hyperprolactinemia. In the present study, among 59 subjects with preoperative hyperprolactinemia, 4 subjects (6.8%) remained sustained hyperprolactinemia at 3 months postoperatively. Postoperative hyperprolactinemia was not related with any other pituitary hormone deficiency ($P = 0.258$ by chi-square test, data not shown). Hence, iatrogenic damage of the pituitary stalk or the entire gland was not the likely cause of postoperative hyperprolactinemia. Other factors such as leukemia inhibitory factor, tachykinin, substance P, and neurokinin A may be related with hyperprolactinemia in NFPAs [18-22]. Further researches are needed to confirm

other factors that can affect hyperprolactinemia in NFPA subjects and the mechanism of these factors.

The present study had several advantages. First, we measured the tumor volume including the three-dimensional diameters, which enable assessment of the relationship between the growth pattern and hyperprolactinemia. Second, we included a relatively large sample size of NFPA subjects who underwent surgery. Third, all operations were performed by the same well-experienced surgeon; therefore, the hormonal outcomes and gross total resection rate were less affected by the surgeon.

Some limitations of this study warrant mentioning. First, owing to a retrospective study design, we could not randomize some factors that could affect hyperprolactinemia before surgery or hormone recovery after surgery, such as age and sex. Hence, we adjusted the confounding factors as covariates in multivariate logistic regression models. In addition, we followed our own specified protocol for pituitary adenomas in most patients, and most data are preserved. Second, insulin tolerance tests for assessing GH deficiency were not performed in some patients with large tumor size, those who were elderly, and those with comorbid conditions. Therefore, GH deficiency can be underestimated. In assessing hormone recovery, GH deficiency was not included.

In conclusion, the present study confirmed a positive correlation between preoperative prolactin level and pituitary tumor width per AP diameter. Higher ratio of tumor width per AP diameter contributed to hyperprolactinemia in NFPA subjects rather than tumor volume. We also found that subjects with preoperative hyperprolactinemia had a higher chance to recover postoperatively. NFPA subjects with hyperprolactinemia may experience a better prognosis than those without hyperprolactinemia. However, further detailed studies are required to validate our findings.

Funding

This study was supported by the grant (No. NRF-2017R1D1A1B03031879 to Kim JH) from National Research Foundation of Korea by the Ministry of Science, ICT and Future Planning (MSIP) of Korea.

A grant (No.: HI16C-1111-020016 to Kim YH) from the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea. A grant (No.: NRF-2017R1A2B2008412 to Kim YH) from National Research Foundation of Korea by the Ministry of Science, ICT and Future Planning (MSIP) of Korea.

Conflict of interest

Nothing to declare.

Acknowledgments

We thank all colleagues who contributed to the study

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Figure 1. Flow chart of study subjects

PRL, prolactin. GKS, gamma knife surgery. IHC, immunohistochemistry.

Figure 2. Scatter plot between serum prolactin level and width/anteroposterior diameter on magnetic resonance imaging

Table 1. Baseline characteristics of study subjects (n=201)

Variables	Values
Men (n, %)	102 (50.7%)
Age (years)	51.1 ± 12.7
BMI (kg/m^2)	25.5 ± 3.5
Tumor AP diameter on MR (mm)	22.6 ± 7.0
Tumor height on MRI (mm)	30.3 ± 7.7
Tumor width on MRI (mm)	26.8 ± 6.3
Maximal tumor diameter (mm)	31.7 ± 7.7
Tumor volume on MRI (cm^3)	10.4 ± 7.7
Cavernous invasion (Knosp Grade ≥ 3)	98 (49.0%)
Preoperative hyperprolactinemia	59 (29.4%)
Preoperative any hormone deficiency	148 (73.6%)
GH deficiency	76 (40.2%)
ACTH deficiency	58 (29.0%)
TSH deficiency	37 (18.7%)
Gonadotropin deficiency	120 (61.2%)
All axes except GH	24 (12.4%)

Data are shown as mean ± standard deviation or n (%). MRI, magnetic resonance imaging.

Table 2. Clinical and hormonal characteristics of subjects with clinically nonfunctioning pituitary adenomas with hyperprolactinemia

Variables	Hyperprolactinemia (-) (n=142)	Hyperprolactinemia (+) (n=59)	***P***
Men (n, %)	86 (60.6%)	16 (27.1%)	<0.001
Age (years)	52.9 ± 12.3	46.7 ± 12.7	0.002
BMI (kg/m^2)	25.7 ± 3.2	24.8 ± 4.1	0.155
Gross total resection	114 (80.3%)	52 (88.1%)	0.257
Preoperative prolactin level	9.7 ± 5.4	43.5 ± 23.4	<0.001
Preoperative hormone deficiency			
GH deficiency	50 (37.9%)	26 (45.6%)	0.404
ACTH deficiency	39 (27.7%)	19 (32.2%)	0.635
TSH deficiency	20 (14.3%)	17 (29.3%)	0.023
Gonadotropin deficiency	77 (56.2%)	43 (72.9%)	0.042
All axes except GH	15 (11.1%)	9 (15.5%)	0.540
Postoperative hormone deficiency			
GH deficiency	80 (59.3%)	35 (62.5%)	0.799
ACTH deficiency	44 (31.7%)	10 (17.2%)	0.059
TSH deficiency	33 (23.4%)	17 (28.8%)	0.531
Gonadotropin deficiency	81 (59.6%)	33 (56.9%)	0.853
All axes except GH	22 (16.4%)	4 (7.0%)	0.133
Postoperative hyperprolactinemia	1 (0.7%)	4 (6.9%)	0.042
Postoperative diabetes insipidus	17 (12.7%)	5 (9.3%)	0.396

Data are shown as mean ± standard deviation or n (%).

Table 3. Logistic regression models of pre-operative prolactin level for predicting hormone recovery in subjects with preoperative ACTH or TSH hormone deficiency (n=135)

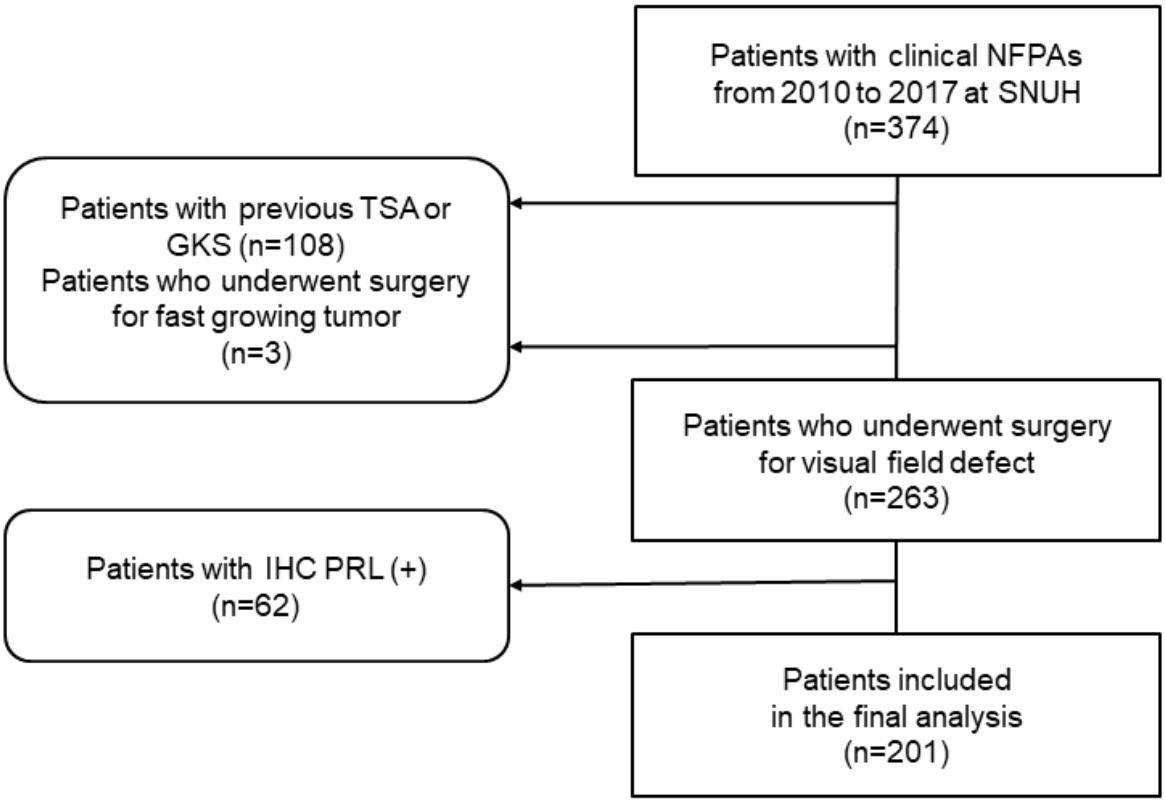
	Unadjusted	Model 1	Model 2
Hyperprolactinemia	2.16 (1.04-4.48)	2.51 (1.01-5.80)	2.55 (1.10-5.92)
Age		0.98 (0.95-1.01)	0.98 (0.95-1.01)
Gender		2.12 (0.94-4.76)	2.11 (0.93-4.75)
BMI		0.97 (0.87-1.08)	0.97 (0.87-1.08)
Tumor volume (per cm^3)			1.00 (0.95-1.05)
Gross total resection			0.79 (0.30-2.12)

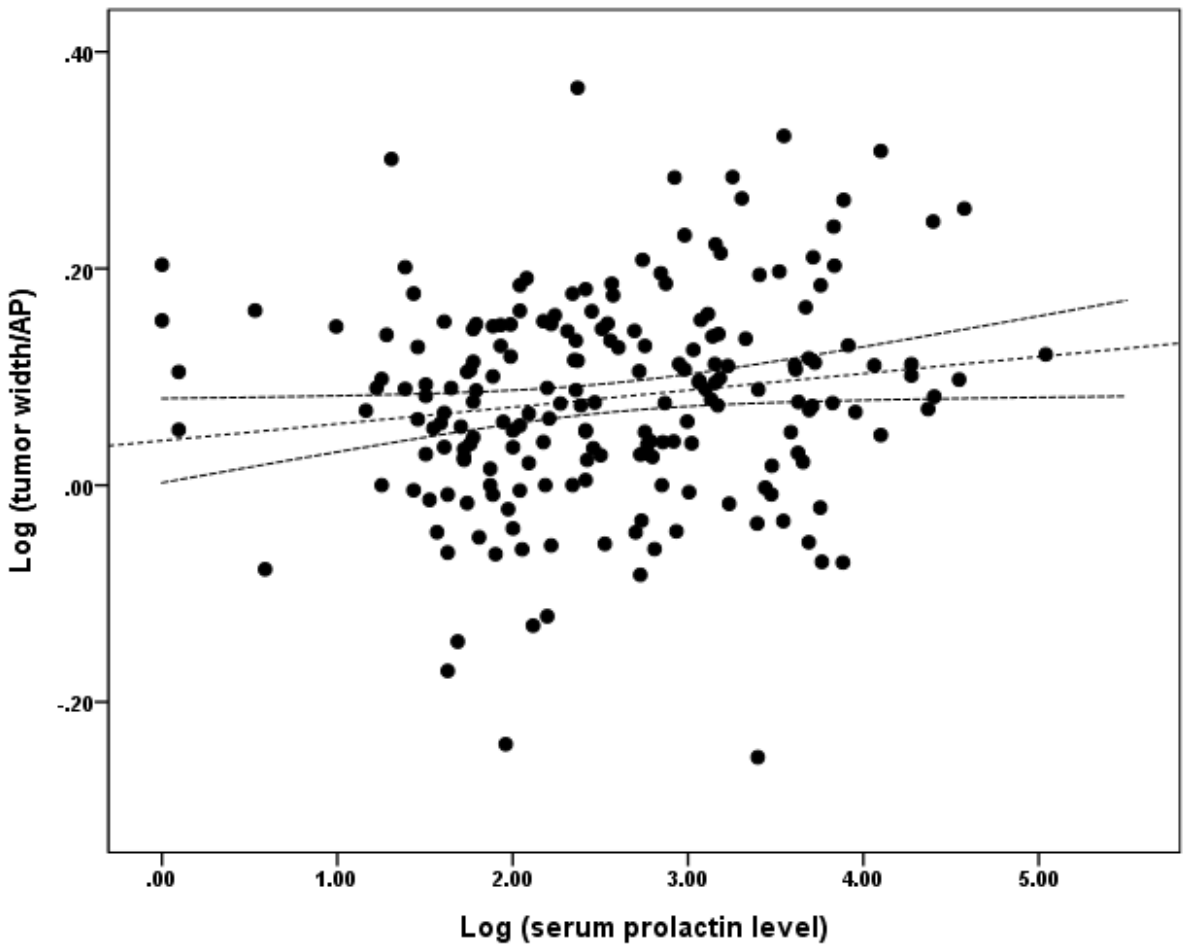
Data are shown as odds ratios (95% confidence interval). Model 1, adjusted for age, gender and BMI; Model 2, further adjusted for tumor volume on MR and gross total resection.

Table 4. Radiographic characteristics of clinically nonfunctioning pituitary adenomas with hyperprolactinemia

Variables	Hyperprolactinemia (-) (n=142)	Hyperprolactinemia (+) (n=59)	***P***
AP diameter on MR (mm)	22.9 ± 6.4	21.7 ± 8.4	0.319
Height on MR (mm)	30.7 ± 8.0	29.2 ± 6.8	0.205
Width on MR (mm)	26.8 ± 6.5	26.9 ± 5.9	0.953
Maximal tumor diameter (mm)	31.9 ± 7.6	31.3 ± 7.9	0.568
Width/AP diameter	1.20 ± 0.26	1.31 ± 0.31	0.014
Height/AP diameter	1.37 ± 0.29	1.41 ± 0.28	0.344
Tumor volume on MR (cm^3)	10.7 ± 7.8	9.6 ± 7.5	0.365
Cavernous invasion	69 (48.6%)	29 (50.0%)	0.980

Prolactin level and tumor diameter on MR are log-transformed. AP, anteroposterior


Patients with clinical NFPAs from 2010 to 2017 at SNUH (n=374)
Patients with previous TSA or GKS (n=108)
Patients who underwent surgery for fast growing tumor (n=3)
Patients who underwent surgery for visual field defect (n=263)
Patients with IHC PRL (+) (n=62)
Patients included in the final analysis (n=201)


.40
.20
.00
-.20
Log (tumor width/AP)
.00
1.00
2.00
3.00
4.00
5.00
Log (serum prolactin level)

Highlights :

Tumor width per AP diameter ratio positively correlated with serum prolactin levels

Tumor volume was not correlated with serum prolactin level

Hyperprolactinemic subjects had a higher chance to recover other hormone deficiency

Hyperprolactinemia is a good prognostic marker for hormone recovery after TSA