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Predictors of testosterone recovery in male patients with nonfunctioning pituitary adenoma treated with transnasal transsphenoidal extrapseudocapsular microsurgery

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Abstract

Aim: To investigate the predictor of hypothalamic-pituitary-gonadal (HPG) axis recovery in male pituitary adenoma patients with trans-sphenoid extrapseudocapsular microsurgery.

Methods: From June 2019 to December 2021, we retrospectively analyzed the clinical data of gonadal hormone changes and resection degree before and after surgery in male patients with nonfunctioning pituitary adenoma (NFPA) who underwent microsurgical resection by pseudocapsule technique in the same treatment group at the Department of Neurosurgery, Tongji Hospital. We explored the predictors affecting postoperative testosterone recovery using logistics regression analysis.

Results: Among 291 male patients with pituitary adenomas, the mean age was 50 years. Preoperative testosterone was lower than normal in 127 patients (43.6%); total resection and subtotal were performed in 279 patients (95.9%) and 12 patients (4.1%), respectively. Postoperative follicle-stimulating hormone (FSH) was elevated in 224 (77.0%) patients, luteinizing hormone (LH) was elevated in 230 (79.0%) patients, and prolactin was significantly decreased in 259 (89.0%) patients. Seventy-one of 127 patients with low preoperative testosterone levels recovered to normal levels. Univariate and multivariate analysis suggested that tumor size, coagulative necrotic pituitary apoplexy (CNPA), and invasiveness were predictors of testosterone recovery in patients ($P < 0.05$).

Conclusion: For male NFPA, transsphenoidal extra-pseudocapsule microsurgery can effectively restore the function of the anterior pituitary gland and promote the recovery of testosterone. Tumor size, CNPA and invasiveness were predictors of testosterone recovery in postoperative patients.

Keywords: Coagulative necrotic pituitary apoplexy, extrapseudocapsular transnasal transsphenoidal surgery, male, pituitary adenoma, testosterone

INTRODUCTION

Pituitary adenoma is a common intracranial tumor with an incidence second only to meningioma and glioma, accounting for approximately 15% of intracranial tumors[1]. Patients often present with clinical manifestations arising from endocrine and mass effects depending on the tumor type[2,3]. In clinical practice, as an indicator for efficacy determination, changes in prolactin (PRL), cortisol, growth hormone, and thyroid hormone often gain more attention, and testosterone is relatively less assessed[4]. Testosterone is a key hormone in the pathology of metabolic dysfunction such as Obesity. Testosterone deficiency is associated with hypogonadism, energy imbalance, impaired glucose control, reduced insulin sensitivity, and dyslipidemia[5]. However, the hypothalamic-pituitary-gonadal (HPG) axis is the most sensitive endocrine axis of the pituitary gland, and therefore, patients with pituitary adenomas often have associated impairment of this axis[6].

HPG axis involvement may be caused by hyperprolactinemia and tumor compression. Hyperprolactinemia may inhibit the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by inhibiting the secretion of gonadotropin-releasing hormone (GnRH), ultimately inhibiting the production of testosterone, and may lead to hypogonadism[7]. Female patients can present early due to elevated PRL, causing irregular menstruation or lactation. Male patients with prolactinomas tend to have larger tumors at presentation and significant mass effects, resulting in low testosterone levels. Some men with other types of pituitary adenomas, such as nonfunctioning pituitary adenomas (NFPAs), tend to have low gonadal hormone test results even in the absence of elevated PRL. This may be because NFPA directly damages anterior pituitary function by compressing the pituitary stalk or gland[2]. Recently, our center analyzed 144 cases of macroadenoma and found that hypogonadism was the most prevalent endocrine dysfunction and had the slowest recovery, regardless of the hormone-secreting activity of functional pituitary adenomas[8].

Except for prolactinomas, trans-sphenoidal microsurgery is still the treatment of choice for pituitary adenomas to relieve compression, correct function, and achieve long-term tumor control[9]. The rise of trans-sphenoidal extra-pseudocapsule resection not only improves the resection rate of surgery, but also plays an important role in preserving pituitary function[4,8,10]. At present, most studies on hypogonadism have been carried out in male prolactinomas. It has been shown that smaller preoperative tumors, lower preoperative PRL levels, faster PRL normalization, and higher preoperative testosterone levels are associated with recovery of the HPG axis in postoperative patients[11]. However, most published studies are highly heterogeneous and findings are poorly generalizable. In addition, there are few studies investigating predictors and mechanisms of HPG axis restoration in patients with NFPA.

Therefore, this study investigated the predictors of postoperative HPG axis recovery in patients with NFPA undergoing extra-pseudocapsule surgical treatment, providing a theoretical basis for the comprehensive treatment of male NFPA patients.

METHODS

Study design and patient population

This study analyzed male patients with NFPA who underwent trans-sphenoidal surgery at the Department of Neurosurgery, Tongji Hospital, from June 2019 to December 2021. All patients were treated with trans-sphenoidal surgery based on extra-pseudocapsule technique by the same experienced neurosurgeon.

Patients who met the following criteria were included in this study: (1) pathologically diagnosed as NFPA; (2) pituitary adenoma was removed using the trans-sphenoidal extra-pseudocapsule technique. Exclusion criteria were (1) incomplete follow-up data; (2) age < 18 years; and (3) a diagnosis of non-central hypogonadism. According to the above criteria, a total of 291 male patients with NFPA were enrolled. Fifteen patients had coagulative necrotic pituitary apoplexy (CNPA) and all of them chose early surgery.

Patient management

All patients underwent sex hormone testing and magnetic resonance imaging (MRI) at our center before surgery. Routine specific surgical procedures for trans-sphenoidal surgery used at our center are described in previously published literature[4,8,12,13].

Hormone evaluation

In all patients, other pituitary hormone tests were performed simultaneously at our center before and after treatment. Hormone levels of patients at the time of admission and three months postoperatively were taken for inclusion in this study. The normal range for testosterone is 1.75 to 7.81 ng/mL. Gonadal hormone testing was performed between 8 and 10 am. The diagnostic criteria for patients with central hypogonadism are low testosterone levels, accompanied by inappropriate normal or low gonadotropin levels.

Testosterone is the most important hormone in this study and is the hormone that most reflects HPG axis function[14]. Inspired by the findings of Zhang *et al.*, we categorized the shifts in testosterone levels into two categories: improved versus unimproved[15].

Radiologic evaluation

MRI examinations were assessed in all patients at our center before and after treatment[4,8]. For patients who underwent surgical treatment, the extent of resection was determined based on the results of preoperative radiological examinations and the first MRI obtained 3 months after surgery, as reported by a neuroradiologist expert. Gross total resection (GTR) was defined as no significant residual enhancing lesion on postoperative MRI.

Patients with CNPA have some characteristic imaging findings, particularly after enhanced scans. Most will present with significant pituitary enhancement signs, and correspondingly, unenhanced parts, especially those encasing one internal carotid artery, are suspicious of invasion[8].

Invasiveness classifications

Tumor invasion was classified according to the method proposed by Lu *et al.*[16,17]. Criteria for evaluation were: (1) radiological invasiveness criteria: Knosp grade 3-4[18]; (2) surgical invasiveness: invasive and destructive growth of the cavernous sinus, sphenoid sinus, clivus, and diaphragm under direct vision during surgery; and (3) histological invasiveness: histological examination revealed invasion and/or destruction of the basal dural samples by pituitary adenomas[19,20]. Pituitary adenoma invasion was classified into the following four grades according to the above evaluation criteria. Grade 0: noninvasive adenoma; Grade I: adenoma meeting one of the three criteria; Grade II: adenoma meeting any two of the three criteria; Grade III: adenoma meeting all three criteria.

Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). According to the distribution characteristics of each type of clinical data, different expression methods and statistical methods were used. Normally distributed continuous variables are presented as mean ± standard deviation, while non-normally distributed variables are presented as median and interquartile range. Categorical variables were compared using the chi-square test or Fisher's exact test. *T*-tests were used to assess differences between normally distributed continuous variables, and Man-Whitney *U*-tests or Wilcoxon Signed Rank tests were used for comparisons between samples of non-normally distributed continuous variables. Logistic regression was used for multivariate analysis. Statistical significance was set at $P < 0.05$.

RESULTS

General clinical characteristics of patients

The mean age of the 291 male patients with NFPA was 50 years (ranging from 18-76 years). Basic patient information is shown in Table 1. Fifteen (5.15%) patients had CNPA. Under the new invasion classification, the highest proportion of patients with invasion grade 0 was 111 (38.14%), and the proportion of patients in the other three groups differed slightly. The overall median values of FSH, LH, PRL, and testosterone were within the normal range.

Preoperative testosterone level and influencing factors

Out of 291 patients, preoperative testosterone was normal in 164 patients (56.36%) and was lower than normal in 127 patients (43.64%). The age, tumor size, PRL, FSH, LH, CNPA. and invasion grade were analyzed in these groups [Table 2]. Univariate analysis showed that tumor size, FSH and LH levels, CNPA, and invasiveness may be factors related to low preoperative testosterone levels ($P < 0.05$).

Further logistic regression analysis of the above factors [Table 3] showed that only preoperative LH level was significantly correlated with preoperative testosterone level ($P < 0.05$).

Postoperative HPG recovery of patients

GTR was performed in 279 patients (95.9%%) and subtotal resection (STR) in 12 patients (4.1%). The level of gonadal hormone levels 3 months after surgery were compared with levels before surgery, as shown in Table 4. Results showed that after extra-pseudocapsule resection, the levels of HPG axis hormones returned to normal levels ($P < 0.05$), FSH, LH, and testosterone levels increased significantly, while PRL levels decreased significantly. Of 291 patients, 224 (77.0%) had elevated FSH, 230 (79.0%) had elevated LH, and 259 (89.0%) had markedly decreased PRL. According to the postoperative testosterone classification criteria, 127 of 291 (43.6%) patients had low preoperative testosterone, in which testosterone levels returned to the normal range at 3-month postoperative follow-up in 71 (55.9%). Postoperative cortisol and thyroid-stimulating hormone (TSH) abnormalities were 5.7% and 6.9%, respectively, and no new permanent hypopituitarism developed.

Adenoma size, invasiveness, predictors of testosterone recovery after surgery, and CNPA

According to the two groups of testosterone changes, patient age, tumor size, preoperative PRL level, FSH, LH level, CNPA, and invasiveness were studied [Table 5]. Univariate analysis showed that tumor size, LH

Table 1. Patient baseline data

Characteristic	Total (*n* = 291)
Age (year)	50 ± 12
Tumor size (cm)	2.38 ± 0.90
Microadenoma, *n* (%)	16 (5.50%)
Macroadenoma, *n* (%)	250 (85.91%)
Giant adenoma, *n* (%)	25 (8.59%)
FSH (mIU/mL)	6.49 (4.10, 9.92)
LH (mIU/mL)	2.87 (1.83, 4.35)
PRL (ng/mL)	11.80 (7.62, 18.76)
T (ng/mL)	2.00 (0.82, 3.07)
CNPA, *n* (%)	15 (5.15%)
Invasion	
Grade 0, *n* (%)	111 (38.14%)
Grade I, *n* (%)	59 (20.27%)
Grade II, *n* (%)	54 (18.56%)
Grade III, *n* (%)	67 (23.02%)

FSH: Follicle-stimulating hormone; LH: luteinizing hormone; PRL: prolactin; T: testosterone; CNPA: coagulative necrotic pituitary adenoma.

Table 2. Univariate analysis of preoperative testosterone levels

Characteristic	Low testosterone (*n* = 127)	Normal testosterone (*n* = 164)	*P*
age (year)	49.6 ± 12.2	50.3 ± 11.5	0.60
Tumor size (cm)	2.63 ± 0.90	2.18 ± 0.85	< 0.001
Hyperprolactinemia, *n* (%)	61 (48.0%)	64 (39.0%)	0.08
FSH (mIU/mL)	4.28 (2.77, 6.88)	8.16 (5.99, 11.16)	< 0.001
LH (mIU/mL)	1.85 (1.09, 2.84)	3.87 (2.70, 5.11)	< 0.001
CNPA (%)	12 (9.4%)	3 (1.8%)	0.004
Invasion			
Grade 0, *n* (%)	33 (26.0%)	78 (47.6%)	
Grade I, *n* (%)	23 (18.1%)	36 (22.0%)	< 0.001
Grade II, *n* (%)	33 (26.0%)	21 (12.8%)	
Grade III, *n* (%)	38 (29.9%)	29 (17.7%)	

FSH: Follicle-stimulating hormone; LH: luteinizing hormone; CNPA: coagulative necrotic pituitary apoplexy.

Table 3. Logistic regression of preoperative testosterone levels

Characteristic	β	Wald	*P* value	OR (95%CI)
Tumor size	0.378	3.210	0.073	1.460 (0.965, 2.208)
FSH	-0.054	1.936	0.164	0.947 (0.878, 1.022)
LH	-0.720	34.121	< 0.001	0.487 (0.382, 0.620)
CNPA	1.174	2.294	0.130	3.233 (0.708, 14.764)
Invasion	-0.256	0.338	0.561	0.774 (0.326, 1.836)

FSH: Follicle-stimulating hormone; LH: luteinizing hormone; CNPA: coagulative necrotic pituitary apoplexy.

level, CNPA, and tumor invasion were factors predicting postoperative testosterone recovery. As shown in Table 6, multiple logistic regression analysis was performed for the above factors, and the results suggested that tumor size, CNPA, and invasiveness could be used as predictors of postoperative testosterone recovery

Table 4. Changes in hormone levels before and after operation

Characteristic	Pre-operation	Post-operation	*P*
FSH (mIU/mL)	6.49 (4.10, 9.92)	8.75 (5.51, 13.09)	< 0.001
LH (mIU/mL)	2.87 (1.83, 4.35)	4.25 (2.90, 6.38)	< 0.001
PRL (ng/mL)	11.80 (7.62, 18.76)	5.20 (2.86, 8.07)	< 0.001
T (ng/mL)	2.00 (0.82, 3.07)	2.78 (1.84, 3.65)	< 0.001

FSH: Follicle-stimulating hormone, LH: luteinizing hormone, PRL: prolactin, T: testosterone.

Table 5. Univariate analysis of testosterone recovery after surgery

Characteristic	Improve (*n* = 71)	No improve (*n* = 56)	*P*
Age (year)	49 ± 13	50 ± 11	0.52
Tumor size (cm)	2.29 ± 0.80	3.06 ± 0.85	< 0.001
Hyperprolactinemia, *n* (%)	39 (54.9%)	22 (39.3%)	0.06
FSH (mIU/mL)	4.68 (2.87, 7.30)	4.28 (2.45, 5.95)	0.26
LH (mIU/mL)	2.08 (1.17, 3.24)	1.46 (1.01, 2.41)	0.03
CNPA (%)	1 (1.4%)	11 (19.6%)	< 0.001
Invasion			
Grade 0, *n* (%)	30 (42.3%)	3 (5.4%)	
Grade I, *n* (%)	16 (22.5%)	7 (12.5%)	< 0.001
Grade II, *n* (%)	17 (23.9%)	16 (28.6%)	
Grade III, *n* (%)	8 (11.3%)	30 (53.6%)	

FSH: Follicle-stimulating hormone; LH: luteinizing hormone; CNPA: coagulative necrotic pituitary apoplexy.

Table 6. Logistic regression of testosterone levels after surgery

Characteristic	β	Wald	*P* value	OR (95%CI)
Tumor size	0.701	3.709	0.04	2.016 (0.988, 4.836)
LH	-0.382	3.756	0.05	0.683 (0.464, 1.004)
CNPA	3.428	8.896	0.003	30.822 (3.240, 293.249)
Invasion	1.584	6.582	0.01	4.872 (1.453, 16.335)

LH: Luteinizing hormone; CNPA: coagulative necrotic pituitary apoplexy.

in male patients ($P < 0.05$).

DISCUSSION

Of the 291 patients who participated in this study, 279 had total resection of the pituitary adenoma and the other 12 had STR. Preoperative testosterone was below normal in 127 (43.6%) and 71 (55.9%) of them recovered to normal levels of testosterone after surgery. Tumor size, CNPA, and invasiveness were predictive factors for testosterone recovery.

HPG axis function is compromised in 60%-93% of patients with pituitary adenomas, particularly macroadenomas[21,22]. Patients with hypogonadism often present with emotional distress, anhedonia, fatigue, and cognitive impairment, all of which are diagnostic criteria for major depression[23]. Studies have shown that testosterone may be associated with depression[24], which can not only regulate serotonergic neurons through kisspeptin neurons to resist depression[25], but also exert antidepressant effects by activating androgen receptors in the hippocampus[26]. Reconstruction of the patient's pituitary endocrine function, including the function of the HPG axis, is therefore the focus of neurosurgeons' attention.

Transsphenoidal extra-pseudocapsule decompression significantly improves HPG axis function

This study showed HPG involvement in 127 of 291 male pituitary adenoma patients (43.6%). Seventy-one (55.9%) patients recovered testosterone levels without developing new hypopituitarism after surgical resection of the tumor via pseudocapsule. A recent study conducted by our research group showed that among 144 patients with pituitary macroadenoma, 51 patients had hypogonadism before surgery and 27 (52.9%) patients had improvement after trans-sphenoidal extra-pseudocapsule surgery. However, other affected hormones recovered to varying degrees without permanent pituitary dysfunction, which is consistent with other reports in the literature[8]. Buchfelder *et al*. reported that the pseudocapsule technique for pituitary adenoma resection did not cause additional anterior pituitary function impairment[13]. Nomikos *et al*. screened 463 patients who underwent conventional trans-sphenoidal surgery for preoperative hypogonadism, and only 74 (15.9%) patients recovered gonadal function 3 months after surgery[12]. Therefore, we hypothesize that the application of pseudocapsule technique may have a significant promoting effect on the recovery of gonadal hormones in male patients after surgery.

Shortening ischemic time is a key factor affecting functional recovery

Our study showed that the size of pituitary adenomas was a predictor of HPG axis recovery in patients after surgery, which is consistent with other reports in the literature[11,27]. A recent publication from our group showed that testosterone improved in 52.9% of 144 patients with pituitary macroadenoma following trans-sphenoidal extra-pseudocapsule surgery. In patients with microadenomas, the HPG axis is less affected in patients[4]. Tumor size plays an important role in causing direct damage to pituitary cells[11]. We believe that tumor size can be used as an indirect indicator to measure pituitary ischemia: the larger the tumor, the more severe the normal pituitary compression ischemia, and the more obvious the preoperative hypopituitarism, so it is difficult for the patient's pituitary function to return to normal immediately after surgical decompression. Zhou *et al*. concluded that when pituitary adenomas are small in size, they have little effect on pituitary function, while total resection of the tumor can be performed by surgery, and gonadal hormone levels mostly return to normal after surgery in patients[28]. Macroadenomas, on the other hand, progressively increase in size, resulting in long-term compression of blood vessels and long-term insufficient blood supply to the pituitary gland, leading to ischemia, and it is difficult for hormone levels to return to normal levels in patients after surgery. Therefore, early surgery and shortening pituitary ischemia time are of positive significance for testosterone recovery.

Early surgery to improve HPG function in patients with CNPA

Our study showed that CNPA is one of the unfavorable factors for HPG axis recovery in patients after surgery. Pituitary apoplexy frequently occurs in patients with macroadenomas and is generally considered a high-risk factor for hypopituitarism[29,30]. CNPA is generally considered a clinical subtype of ischemic pituitary apoplexy with unique intraoperative cosmetic appearance as well as histopathological features[30,31]. CNPA generally has a slower onset and a longer time to compress the pituitary gland, so the recovery time of anterior pituitary function is also longer[30,31]. Our study showed that testosterone levels improved in only 1 of 12 CNPA patients (1.4%) and were maintained in 11 of 12 CNPA patients (19.6%), all of whom chose aggressive early surgical treatment after presentation, and testosterone recovery remained significantly worse than in patients without CNPA. Therefore, we suggest that the poor pituitary function prognosis in CNPA patients may be related to irreversible pituitary damage caused by pathological changes such as compression and ischemic necrosis.

At present, there is still a lack of consensus on the optimal operation time for pituitary apoplexy; some believe that early surgery is beneficial for the recovery of neurological and endocrine function in patients and should be actively selected[30]. Rajasekaran *et al.* systematically classified the surgical indications for pituitary apoplexy[32], but Jho *et al.* stated that early aggressive surgical treatment should be as relaxed as possible[33]. Previous studies have also indicated that early surgery can relieve compression of local structures and provide improved endocrine and neuro-ophthalmologic outcomes[31], similar to the viewpoint of our group. However, the specific impact of the various timing of surgeries on gonadal hormone recovery efficiency requires further verification through more central studies.

Since serum PRL can inhibit the pulsatile release of anterior pituitary gonadotropins, leading to secondary hypogonadism and directly affecting spermatogenesis[34], early studies on testosterone recovery have primarily focused on males with PRL adenomas who were treated with oral dopamine agonists (DAs), which generally had significantly elevated PRL, and have proposed that PRL levels have a significant impact on gonadal function recovery[11,27,35]. In contrast, at relatively low levels in our study, PRL did not significantly affect testosterone recovery.

In this study, we found that tumor invasiveness could prevent the improvement of the HPG axis in patients after surgery, similar to some previous findings[28]. Invasive pituitary adenomas often invade and grow outside the pseudocapsule, resulting in pseudocapsule rupture or bleeding[36], while making intraoperative total resection difficult and hormone response unsatisfactory[13,20]. Indeed, improvement can be made using intraoperative MRI to identify intraoperative residual conditions[37-39]. However, pseudocapsule can often be found between the normal pituitary gland and the tumor, which may protect the normal pituitary gland and reduce pituitary gland injury during surgery, allowing the pituitary function to partially recover after surgery. However, invasive pituitary adenomas tend to have residual tumors after surgery and are a recurrent factor, and complete resection with follow-up is significant in the first surgery[12].

As this is a single-center study, it is difficult to adequately present the relevant characteristics of a larger sample of male patient populations, which is a limitation of this study. In our study population, the number of patients who underwent surgery for prolactinoma was relatively small. In addition, data on hormone tests did not contain information on sex hormone binding globulin and serum free testosterone results, which may be more beneficial if further assessment of sexual function in male patients is required.

DECLARATIONS

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Authors' contributions

Conceptualization: Zhang H, Shu K, Lei T
Data curation: Zhang Z
Investigation: Lu L
Methodology: Wan X
Resources: Xu Y
Software: Chen J
Writing - original draft: Yan Z
Writing - review and editing: Wan X, Lei T

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

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Conflicts of interest
Lei T is an Editor on the Editorial Board of the journal *Metabolism and Target Organ Damage*. Lei T was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. The other authors declared that there are no conflicts of interest.

Ethics approval and consent to participate
This research was approved by the Tongji Hospital research ethics committee. The ethical approval number for the study is TJ-IRB20211166. For this type of study, formal consent was not required.

Consent for publication
Not applicable.

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