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The Relationship Between Posterior Pituitary Bright Spot on Magnetic Resonance Imaging (MRI) and Postoperative Diabetes Insipidus for Pituitary Adenoma Patients

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Background: This study is to investigate the predictive value of posterior pituitary bright spot (PPBS) on magnetic resonance imaging (MRI) for postoperative diabetes insipidus (DI) in patients with pituitary adenoma.





Material/Methods: This was a retrospective study. In total, 65 patients with pituitary adenoma who underwent transsphenoidal surgery were enrolled. Before surgery, all patients had MRI examinations. The length of pituitary stalk and position of PPBS in T1WI sagittal and coronal sections were analyzed. The volume and height of the tumor was calculated in enhanced T1WI. Urine volume was monitored to analyze the clinical factors contributing to DI.

Results: Among the 65 cases of pituitary adenoma, there were 54 cases of positive PPBS and 11 cases of negative PPBS. There were 32 cases of transient DI, and among these, 22 cases were positive PPBS and 10 cases were negative PPBS. However, there were 33 cases without DI, and among these, 32 cases were positive PPBS and one case was negative PPBS. The negative PPBS was significantly higher in cases with DI, compared with positive PPBS ($P < 0.05$). Logistic regression showed that preoperative negative PPBS was an important predictor for postoperative DI ($P < 0.05$).

Conclusions: Postoperative DI should be considered when there is negative preoperative PPBS on MRI. Also, severe pituitary stalk compression indicates higher risk of postoperative DI.

MeSH Keywords: **Diabetes Insipidus • Magnetic Resonance Imaging • Pituitary Diseases • Secreting Pituitary Adenoma**

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Background

Pituitary adenoma is the most common type of sellar lesions, accounting for 10% to 15% of intracranial tumors [1]. Transsphenoidal surgery is the primary treatment for pituitary adenoma [2]. Diabetes insipidus (DI) is one of the common complications after transsphenoidal pituitary adenoma resection surgery, with occurrence rate of 1% to 67% [3]. DI may be caused by compression or destruction of the posterior pituitary gland, interruption of the blood supply to the gland or edema of the pituitary stalk [4]. Uncontrolled DI leads to hypernatremia and high osmotic pressure, or even dehydration, lethargy, psychosis, and severe seizures [5].

An area of T1 hyperintensity is normally observed in the posterior part of the sella turcica on magnetic resonance imaging (MRI) of the brain. This phenomenon is often referred to as the pituitary posterior bright spot (PPBS) [6]. PPBS is well-characterized and is thought to be the imaging correlate of membrane-bound secretory vesicles containing anti-diuretic hormone (ADH) in the neurohypophysis [7]. The PPBS should be between 1.2 mm and 8.5 mm in its longest axis and between 0.4 mm and 4.4 mm in the axis perpendicular to the longest axis in patients who do not have any pituitary abnormality [6]. Little is known about the potential relationship between the preoperative site of ADH storage and the occurrence of postoperative DI [8]. Currently, factors contributing to postoperative DI remain controversial [3], and further knowledge of DI after pituitary adenoma surgery would improve its perioperative management. In this study, 65 cases of patients with pituitary adenoma were analyzed retrospectively to explore the diagnostic value of PPBS on MRI for postoperative DI.

Material and Methods

Patients

Sixty-five patients with pituitary adenoma were recruited from March 2014 to March 2015 from Department of Neurosurgery, Fuzhou General Hospital. Of the 65 cases, there were 32 males and 33 females with age ranging from 19 to 72 years and mean age of 46.8 ± 12.5 years. The inclusion criteria included: 1) patients who underwent transsphenoidal pituitary adenoma resection surgery; 2) surgery was performed by the first author in this paper; and 3) cases with complete preoperative and postoperative data (age, gender, tumor volume and height, presence of cerebrospinal fluid leak, the cavernous sinus invasion, the skull base invasion, suprasellar extension, and immunohistochemistry type). The exclusion criteria included: 1) history of pituitary surgery or radiation treatment; 2) cases accompanying other type of sellar diseases (e.g., pituitary adenoma case with Rathke's cleft cyst). The major clinical manifestations

included: headache, amenorrhea–lactation syndrome, blurred vision, acromegaly, and decreased libido, with no polydipsia or polyuria. According to the “platform-like volume calculation formula” [9], the tumor volume of patients ranged from 0.4 cm^3 to 24.3 cm^3 with the average volume of $6.53 \pm 5.97 \text{ cm}^3$, and tumor height of patients ranged from 9 mm to 51.8 mm with the average height of 23.5 ± 10.9 mm. Postoperative immunohistochemical staining showed that there were 12 cases of null cell adenoma, 20 cases of prolactin type, 14 cases of pluri-hormonal type, 13 cases of gonadotropin type, 1 case of growth hormone type, 2 cases of adrenocorticotrophic hormone type, and 3 cases of thyroid stimulating hormone type. Prior written and informed consent were obtained from every patient's family and the study was approved by the ethics review board of Fujian Medical University.

MRI analysis

All patients had MRI before and after surgery using Siemens 3.0T MRI machine (Siemens Medical Solutions, Erlangen, Germany). T1W1 axial, sagittal, and coronal scans and enhanced scans were performed. Scan field of view was 180×180 mm with matrix of $320\text{--}384 \times 240\text{--}252$, axial slice of 1.0 mm, gap of 1.0 mm, coronal and sagittal section of 1.0 mm with gap of 1.0 mm. After plain MRI scan, patients remained in the same position for enhanced 3-dimensional scan, using contrast agent of gadolinium-DTPA (Gd-DTPA) with a dose of 0.2 mmol/kg body weight. MRI results were analyzed by 2 doctors, one from the Department of Radiology and 1 doctor from the Department of Neurosurgery, with special attention on PPBS.

Signal ratio of PPBS to mesencephalon

On sagittal section of MRI-T1WI, the size and signal strength of the largest PPBS section was analyzed by INFINITT PACS medical imaging system (INFINITT Healthcare Co., Ltd, Seoul, Korea). The 5 mm circular area in pons was analyzed for signal strength. The signal ratio was defined as the signal ratio of PPBS to pons [10] (Figure 1).

The location of PPBS

PPBS was carefully identified in sagittal and coronal section of MRI-T1WI. The PPBS position was categorized as at the supradiaphragmatic portion, in the sella, both in the sella and along the distal pituitary stalk (Figure 2).

The compression ratio of pituitary stalk

The compression ratio (CR) of pituitary stalk, i.e., the ratio of the vertical length of the stalk (a) divided by the estimated normal length of the stalk (b), was determined. The normal length was determined by the distance from the optic

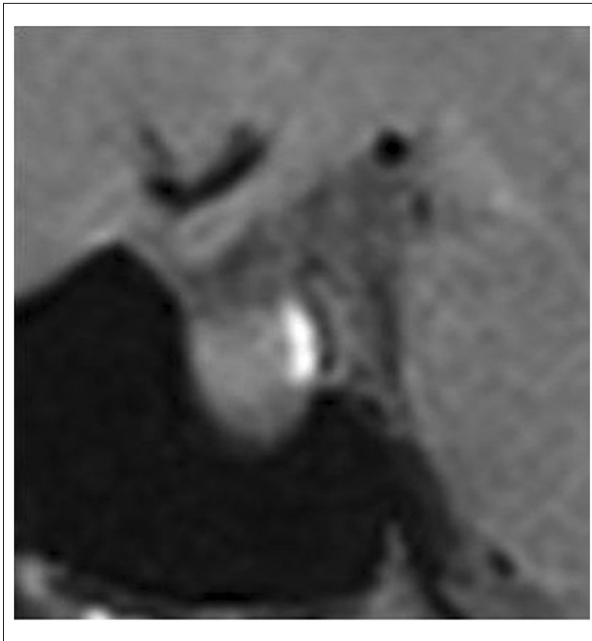


Figure 1. Measurement of area and signal ratio of posterior pituitary bright spot (PPBS) on magnetic resonance imaging T1W1 sagittal sections. The area of PPBS was 9.13 mm². Average signal intensity (Avg) ratio of PPBS to pons was 567.13/305.89=1.85.

chiasm to the lateral attachment of the diaphragma sellae [11]. When the tumor touched the bottom of the chiasm, causing obliteration of the stalk, CR=0. In cases where the chiasm was displaced upward, the CR was defined as “negative” ($CR=-a/b$) and was the distance from the lateral (lowest) margin of the chiasm to the top of the tumor divided by the distance from the lateral margin of the chiasm to the lateral attachment of the diaphragma (Figure 3).

Calculation of tumor volume

In enhanced coronal T1WI, the tumor volume of scanned images was calculated based on the “platform-like volume calculation formula” [9]. Tumor volume in each section was calculated

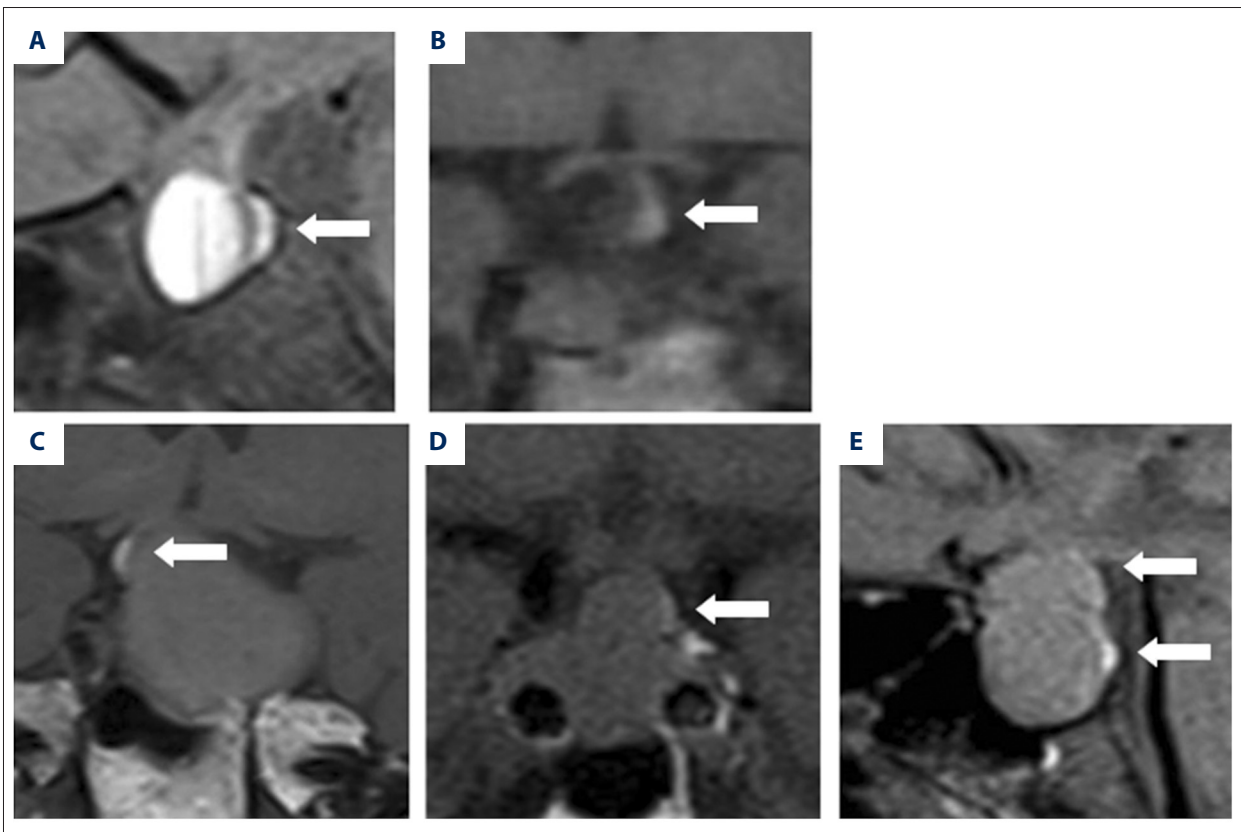


Figure 2. Posterior pituitary bright spot (PPBS) location of pituitary adenoma patients on magnetic resonance imaging (MRI) T1WI. (A) MRI, sagittal showed PPBS located in the sella; (B) MRI, coronal showed PPBS located at the supradiaphragmatic portion (middle); (C) MRI, coronal showed PPBS located at the supradiaphragmatic portion (right); (D) MRI, coronal showed PPBS located at the supradiaphragmatic portion (left); and (E) MRI, sagittal showed PPBS located both in the sella and along the distal pituitary stalk. White arrow: PPBS.

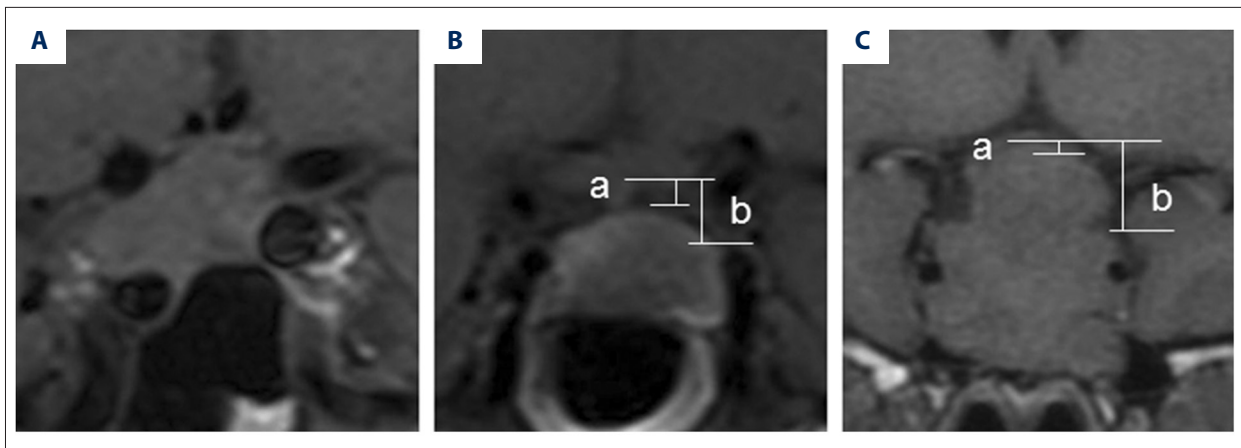


Figure 3. The pituitary stalk compression ratio (CR) of 3 cases on magnetic resonance imaging T1WI coronal section. (A) Tumor touching the lower edge of optic chiasm ($CR=0$); (B) Tumor not touching optic chiasm ($CR=a/b$); and (C) Tumor compressing optic chiasm ($CR=-a/b$).

and accumulated for final volume. Although individual layer cannot represent the whole volume, its final result is closer to the actual volume compared with conventional formula, with significantly reduced errors, especially in tumor with irregularly shape [12].

Diagnostic criteria for DI

In this study, Kinoshita's [13] diagnostic criteria on DI was used, including 1) the urine volume of continuous 2-hour was greater than 600 mL, or the 24-hour urine volume was greater than 2500 mL; 2) specific gravity of urine was less than 1.005; and 3) anti-diuretic medication was needed.

Statistical analysis

SPSS18.0 (SPSS Inc, Chicago, IL, USA) statistical software was used for analysis. Measurement data was presented as mean \pm standard deviation. Group comparisons or comparisons of 2 independent samples used *t*-test or Wilcoxon rank sum test. Categorical data were presented as percentages and were compared using χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Postoperative DI

In this study, urine volume and urine specific gravity of 65 pituitary adenoma cases were analyzed to determine the diagnosis of DI using the aforementioned diagnostic criteria. Among the cases, there were 32 cases of postoperative DI (49.2%), all of which were transient DI. There were 19 cases (29.2%) of transient DI on the first day after surgery, 32 cases (49.2%) on the second day, 27 cases (41.5%) on the third day, 19 cases (29.2%)

on the fourth day, 16 cases (24.6%) on the fifth day, 5 cases (7.7%) on the sixth day, and 3 cases (4.6%) on the seventh day. The 29 cases of DI were resolved at 1 week after surgery. All patients took oral desmopressin in the hospital, while 3 cases continued taking oral desmopressin after discharge. Their urine volume was normal after 1–3 months of follow-up, and thus desmopressin was stopped. These results indicate that permanent DI was of low probability for pituitary tumor patients after transsphenoidal surgery. The reported prevalence of permanent DI ranges from 0.5% to 15% [14]. There were no cases of DI that could not be controlled with drugs in this study. Electrolyte changes should be closely monitored before and after surgery to prevent DI associated dehydration.

Relationship between positive PPBS and postoperative DI

To analyze the relationship between positive PPBS and postoperative DI, group comparison was performed between cases with and without postoperative DI. There were 54 cases of positive PPBS, including 22 cases of postoperative transient DI. The average PPBS signal strength ratio was 1.58 ± 0.26 , with average PPBS area of 5.89 ± 3.98 mm² on sagittal section of MRI. There were 32 cases without DI with average PPBS signal strength ratio of 1.62 ± 0.30 and average PPBS area of 8.23 ± 9.30 mm² on sagittal section of MRI. There were no significant differences in signal intensity ratio and average area between cases with and without DI (Table 1). There were 11 cases of negative PPBS, and of these, 10 cases had transient postoperative DI. Negative PPBS was associated with DI with significant differences (Table 2). The location of positive PPBS in 54 cases is shown in Table 3. There was no significant difference between PPBS location and postoperative DI ($P=0.847$). Therefore, patients with negative PPBS had higher risk of postoperative DI, while in patients with positive PPBS,

Table 1. The signal intensity ratio and area comparison of preoperative PPBS for cases with and without diabetes insipidus (x±s).

	Diabetes insipidus (n=22)	No diabetes insipidus (n=32)	Z	P
PPBS signal intensity ratio	1.58±0.26	1.62±0.30	-0.548	0.586
PPBS area in sagittal section (mm ²)	5.89±3.98	8.23±9.30	-1.470	0.140

Wilcoxon rank sum test was used.

Table 2. Correlation analysis of postoperative diabetes insipidus (x±s).

		Diabetes insipidus (n=32)	No diabetes insipidus (n=33)	Correlation	P
Gender(n)	Male	14	18	0.758	0.384
	Female	18	15		
Age (years)		48.1±10.5	45.4±13.9	0.855	0.396
Tumor volume (cm ³)		7.63±5.56	26.0±10.9	-1.825	0.068
	0–10 cm ³	22	28	2.372	0.124
	10–20 cm ³	10	5		
Tumor height (mm)		5.56±6.16	21.3±10.4	-1.621	0.105
	0–10 mm	2	2	0.416	0.812
	10–30 mm	20	23		
	>30 mm	10	8		
PPBS (n)	Positive	22	32	9.202	0.002
	Negative	10	1		
Cerebrospinal fluid leak (n)	Yes	7	4	1.099	0.294
	No	25	29		
Cavernous sinus invasion (n)	Yes	20	18	0.423	0.515
	No	12	15		
Skull base invasion (n)	Yes	10	12	0.190	0.663
	No	22	21		
Suprasellar extension (n)	Yes	26	25	0.290	0.590
	No	6	8		
Pituitary stalk (n) compression ratio	Negative	23	15	4.67	0.031
	Positive	9	18		
Immunohistochemistry types	Prolactin type	8	12	1.146	0.766
	Null cell type	6	6		
	Plurihormonal type	8	6		
	Gonadotropin type	7	6		

χ^2 test was performed for comparison of gender, tumor volume and height, PPBS, pituitary stalk compression ratio, cerebrospinal fluid leak, cavernous sinus invasion, skull base invasion, suprasellar extension. Wilcoxon rank sum test was used for comparison of age, tumor volume and height.

Table 3. Association between PPBS position and diabetes insipidus for 54 pituitary adenoma patients with positive PPBS.

PPBS position	Diabetes insipidus (n=22)	No diabetes insipidus (n=32)	χ^2	P
In the sella (middle)	9	16	1.381	0.847
In the sella (left and right)	2	3		
At the supradiaphragmatic portion (middle)	4	4		
At the supradiaphragmatic portion (left and right)	5	8		
Both in the sella and along the distal pituitary stalk	2	1		

χ^2 test was used.

Table 4. Multivariate logistic regression of risk factors for postoperative diabetes insipidus.

	B	Standard error	Wald	P value	Exp(B)	95% Exp(B)
Pituitary stalk compression ratio	0.184	0.534	0.119	0.730	1.202	0.423–3.422
Negative PPBS	-2.631	1.092	5.801	0.016	0.072	0.008–0.613

Multivariate Logistic regression was used with pituitary stalk compression ratio and negative PPBS as independent variables. It showed negative PPBS is a predictor for postoperative diabetes insipidus.

the PPBS location had no obvious predictive value on presence of postoperative DI.

Comparison of cases with and without postoperative DI

To determine the differences between cases with and without postoperative DI, their clinical characteristics were analyzed. There was no statistical difference in age, gender, tumor volume and height, presence of cerebrospinal fluid leak, cavernous sinus invasion, skull base invasion, suprasellar extension or immunohistochemistry types between cases with and without postoperative DI. The preoperative positive PPBS rate was significantly lower in cases with postoperative DI than those without ($P=0.002$). The pituitary stalk CR of positive PPBS cases was significantly larger than those of negative PPBS ($P=0.031$) (Table 3). The results showed that for postoperative DI cases, they were most likely with negative PPBS and negative pituitary stalk CR.

Multivariate logistic regression of transient postoperative DI

To determine the risk factors of postoperative DI, the factors of pituitary stalk compression ratio and negative PPBS were used as independent variables, and DI was used as dependent variable for logistic regression. The result showed that negative PPBS was a risk factor for postoperative DI (Table 4). These results also indicated that preoperative negative PPBS cases were more prone to postoperative transient DI.

Discussion

Postoperative DI may present as transient DI, permanent DI, or triphasic DI [3,15]. Most transient DI appears within 24 to 48 hours after surgery and gradually resolves over several days. In this study, the incidence of DI was 49.2%. The majority of the cases resolved in 1 week while a few cases resolved within 1 to 3 months. Postoperative permanent DI is relatively rare in patients with pituitary adenoma [14]. Mortini et al. [16] reported that permanent DI occurred in 0.9% of patients. Permanent DI occurs when there is loss of 85% or more of the hypothalamic magnocellular neurons. The closer the surgical injury is to the hypothalamus, the more likely neuronal degeneration and cell death will arise [3]. There were no permanent DI cases in this study.

One study reported that the signal intensity of the posterior lobe of the pituitary gland on T1-weighted images was significantly higher in females than in age-matched males and that the estimated signal intensity for males and females decreased constantly with age at 1.7% per decade [10]. Liu et al. [17] found no difference in the risk of postoperative DI between elderly and younger patients. However, this study found that there was no significant difference in gender and age between groups with and without DI, suggesting that age and gender are not risk factors for postoperative DI in patients with pituitary adenoma.

There is no consistent conclusion on the relationship between intraoperative cerebrospinal fluid leak and postoperative DI.

An intraoperative cerebrospinal fluid leak may simply be a marker for a more aggressive resection involving more stalk manipulation, and inflammatory process after the reconstruction of the sellae may also promote an increased risk of transient DI [18]. These may explain the finding that the incidence of transient DI is high in patients who have an observable intraoperative CSF leak. However, Chowdhury et al. [19] found no relationship of postoperative DI with cerebrospinal fluid leak, which is consistent with the results of this study.

There is no consensus of whether pituitary adenoma volume is associated with postoperative DI. Sigounas et al. [20] showed that there was no association between tumor volume and DI. However, Nemergu et al. [18] reported that complete excision of microadenomas required more manipulations that may damage the posterior pituitary and pose greater risk for postoperative DI. Lee et al. [21] believed that larger tumor volume required more manipulations that may damage posterior pituitary or pituitary stalk. In this study, tumor volume was accurately calculated, and we found that there was no significant difference in tumor volume between groups with or without DI. Meanwhile, tumor volume had no obvious impact on the incidence of postoperative DI. These results suggest that there is no association between tumor volume and DI incidence.

In this study, univariate analysis showed that there was no significant difference in tumor height between groups with and without DI, however, there was significant difference in pituitary stalk CR. Therefore, pituitary stalk CR can better predict postoperative DI, compared with tumor height. Tumor height only represents the vertical diameter of the tumor while the pituitary stalk CR indicates the tumor growth above the sellae. When CR is negative, tumor compresses optic chiasm and thus the risk of surgery damaging pituitary stalk and posterior pituitary is greater. After transsphenoidal surgery, diaphragma sella would sink that pituitary stalk would be dragged down and stretched, leading to less blood delivery and reduced neuroendocrine particles delivery within the axon. Therefore, for optic chiasm compressed patients with negative CR, surgeons should be more careful in the operation because postoperative DI is more likely to occur.

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Studies have shown that high signal of posterior pituitary may indicate ADH content [22,23]. Bonneville et al. [8] believed that the further PPBS position was away from sphenoid and the closer to the hypothalamus, the less likely PPBS was injured in transsphenoidal surgery. Thus, postoperative DI incidence was lower. However, currently there is no study to support this theory. In our study, we found that the negative PPBS group was more prone to postoperative transient DI. For the positive PPBS group, there was no statistical significance in postoperative DI occurrence for patients with different PPBS size, signal intensity ratio and position. Multivariate logistic regression analysis showed that negative PPBS was a predictor for postoperative DI. PPBS shows ADH storage in the posterior pituitary, and central DI resulted from lack of ADH synthesis or release. Thus, PPBS is often negative in these patients. For pituitary adenoma patients with negative PPBS, no preoperative DI indicates complete function of neurohypophysis with equal speed of ADH synthesis and release, and the bright signal disappears in a depleted posterior where vasopressin storage is markedly decreased due to persistent vasopressin hypersecretion [24]. In this study, positive PPBS showed larger reserve of ADH in neurohypophysis and postoperative DI was less likely.

This study had some limitations. First, it was a single center retrospective study with a relatively small group of patients. Second, no case of permanent DI was included in this study. Larger multicenter studies are necessary to investigate the predictive value of PPBS on MRI for postoperative DI in the future.

Conclusions

By identifying the presence and position of PPBS in pituitary adenoma patients, surgeons can protect PPBS intentionally in surgery, thus reducing the neurohypophysis damage. For patients with negative PPBS, neurohypophysis is hard to identify, thus posing greater surgical risk and greater probability of DI. Also, severe pituitary stalk compression indicates that postoperative DI is more likely to occur.

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