RESEARCH

Change in the pituitary stalk deviation angle after transsphenoidal surgery can predict the development of diabetes insipidus for pituitary adenomas

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Abstract

Purpose: We aimed to assess the factors influencing the development of diabetes insipidus after transsphenoidal surgery for pituitary adenomas.
Methods: A retrospective analysis was conducted on the clinical data of patients with pituitary adenomas who underwent transsphenoidal surgery. The predictors of postoperative diabetes insipidus were determined using statistical analysis.
Results: Of the 415 patients who underwent microscopic transsphenoidal surgery for pituitary adenomas, 196 experienced postoperative diabetes insipidus. The sinking depth of the diaphragma sellae and the difference between the preoperative and postoperative pituitary stalk deviation angles in the diabetes insipidus group were greater than those in the non-diabetes insipidus group. Logistic regression analysis showed that the risk of diabetes insipidus after transsphenoidal surgery was higher in patients with a larger difference in their pituitary stalk deviation angles (odds ratio = 2.407, 95% CI = 1.335–4.342; $P = 0.004$).
Conclusion: The difference in the pituitary stalk deviation angle could predict the onset of diabetes insipidus after transsphenoidal surgery for pituitary adenomas.

Key Words

- diabetes insipidus
- transsphenoidal surgery
- pituitary adenomas
- pituitary stalk
- diaphragma sellae

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Introduction

Most pituitary adenomas (PAs) can be treated surgically using a transnasal approach; experienced clinicians can perform this surgical method effectively, ensuring safety for patients. However, diabetes insipidus (DI) is a common complication following transsphenoidal surgery (TSS) (1, 2), and the clinical management of DI depends greatly on the clinician's experience with DI. Failure to treat DI quickly can lead to hyperosmolar dehydration with corresponding clinical manifestations, including irritability, hypoesthesia, epilepsy, coma, hypotension, acute tubular necrosis, and renal failure (3).

The mechanisms of DI after TSS for PAs include mechanical damage to the hypothalamus, pituitary stalk, and posterior pituitary (4). The large neurons of the supraoptic and paraventricular nuclei of the hypothalamus synthesize antidiuretic hormone (ADH) and transport it along the hypothalamic–pituitary tract to the posterior pituitary, where it is stored and secreted into the blood (5, 6). When the hypothalamic–neurohypophyseal system is mechanically damaged, the synthesis or secretion of ADH is impaired and transient or permanent DI may occur. Because it is usually impossible

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to inspect the pituitary stalk or posterior pituitary directly during TSS, it is also difficult to assess the degree of damage to the hypothalamic–neurohypophyseal system. Therefore, relevant literature only reports the predictive factors of postoperative DI.

The current predictors of the occurrence of DI after TSS are cephalocaudal tumor diameter (7), intraoperative cerebrospinal fluid (CSF) leakage (8), microadenoma (8), nonvisible posterior pituitary bright spot (PPBS) (9), age < 65 years (4), total tumor resection (4), the presence of visual abnormalities (10), suprasellar extension (10), maximal tumor diameter (10), and gross total surgical resection and tumor size (> 1 cm) (11). Notably, various research centers have not reached a consensus on the predictive factors of DI after TSS. Apart from a study that presented a direct injury to the hypothalamic–neurohypophyseal tract during operation as a predictive factor of DI, no other reports on the mechanisms of injury exist.

The main aim of this study was to assess the factors influencing the development of DI after TSS for PAs. To this end, we established the following objectives: (i) retrospective data collection; (ii) observation of the elevation of the diaphragma sellae (DS) and changes in the pituitary stalk deviation angle; and (iii) investigation of the relationship between the DS, pituitary stalk, and postoperative DI. Furthermore, we aimed to propose a novel possible mechanism of damage of DI after TSS.

Materials and methods

Patient cohort

A retrospective analysis was conducted on the clinical data of patients with PA who underwent TSS in our Neurosurgery Department between January 2012 and January 2022. This study was approved by the Ethics Committee of the 900th Hospital, and the patients gave consent to use their clinical data for research purposes, and all data were anonymized.

We included patients who underwent (i) microscopic TSS for PAs, (ii) surgery for the first time, and (iii) repeated MRI examinations 2–3 days after surgery. We excluded patients who had a preoperative history of (i) radiotherapy and (ii) pituitary surgery. Patients were divided into DI and non-DI groups.

Radiological evaluation

Each pituitary gland was scanned using the Siemens Tim Trio 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) to acquire sagittal and coronal images. The potential factors for postoperative DI included the sinking depth of the DS; tumor height, volume, and invasiveness; intratumoral cysts or hematomas; the occurrence of PPBS; the location of PPBS; the extent of tumor resection; pituitary stalk deviation angle; and the imaginary angle drawn between the beginning of DS elevation and its highest point (Fig. 1). The angle at the point where the pituitary stalk started to deviate from the midline was considered the deviation angle of the pituitary stalk (12) (Fig. 2). The difference between the preoperative and postoperative pituitary stalk deviation angles (i.e. the pituitary stalk deviation angle difference) was measured (13). The difference in the pituitary stalk deviation angles was categorized into three groups: 0 ≤ angle < 30°, 30°≤ angle < 60°, and 60°≤ angle < 90°. The DS appears as a thin, short-line, low-signal structure on T2-weighted imaging (14). We followed the methods of Wang *et al.* to measure the sinking depth of the DS (13) (Fig. 3). Tumor volume was calculated using the platform-like volume calculation formula (15). Patients with Knosp grade 3 or 4 were defined as having cavernous sinus invasion (16). The extent of tumor resection was classified as total resection, subtotal resection, and partial resection (17). The saddle tuberosity dorsum sellae was divided into upper and lower parts to locate the PPBS. MRI indications were evaluated by a neurosurgeon (XL) and neuroradiologist (CJ) who were blinded to the clinical outcome, and the average value was recorded. Disagreements regarding imaging findings were resolved through discussion until consensus was achieved.

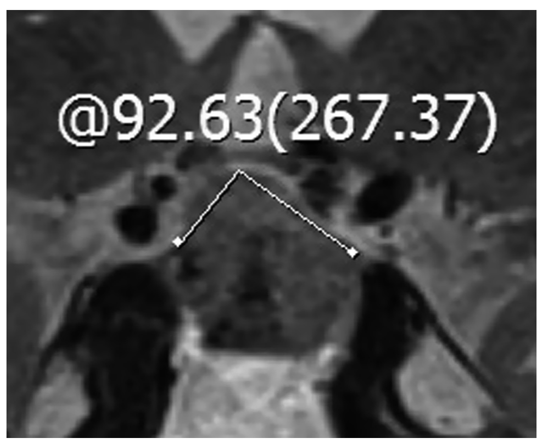

Figure 1
The imaginary angle between two edges of the diaphragma sellae: the beginning of its elevation and its highest point.

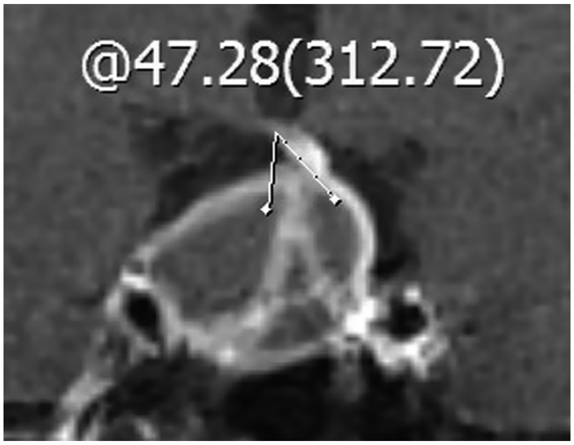

Figure 2
Coronal contrast-enhanced images of the pituitary stalk deviation angle before transsphenoidal surgery. The pituitary stalk is deviated 47.28° to the left.

Diagnostic criteria for DI

The diagnostic criteria for DI were as follows: (i) polyuria (urine production >300 mL/h for 3 h); (ii) urine specific gravity < 1.005; and (iii) at least 1 of the following symptoms: thirst (patient complaint), serum osmolality > 300 mOsmol/kg, or serum sodium > 145 mmol/L (5). All patients were observed in the hospital 6–7 days after surgery to assess whether there were any complications. For those who need active medical intervention, the hospital stay was prolonged. We followed up for at least 6 months for the evaluation of DI.

Statistical analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics for Windows, version 20 (IBM) and R software (Version 4.2.1; https://www.R-project.org). Qualitative variables are represented by the number of patients and percentiles, and quantitative variables are represented by the median (interquartile range). The independent samples *t*-test, Wilcoxon rank-sum test, Fisher's exact test, chi-square test, Spearman correlation analysis, and logistic regression analysis were applied. Factors predictive of DI in the univariate analysis ($P < 0.05$) were entered into a stepwise binary logistic regression model to identify independent factors for DI. Receiver operating characteristic (ROC) curves and the area under the curve were obtained to validate the logistic regression model. $P<0.05$ was considered statistically significant.

Results

Patient demographics

During the study period, 663 patients with PAs underwent TSS. Ultimately, 415 eligible patients were included in the study. Our cohort included 216 men and 199 women with a mean age of 48.7 ± 13.3 years. Among the included patients, 236 (56.9%) had functioning adenomas and 51 (12.3%) had invasion into the cavernous sinus. Demographic data are summarized in Table 1.

Postoperative DI

Of the 196 patients (47.2%) with postoperative DI, 8 developed hypernatremia that lasted for 1–2 days; the highest blood sodium level among these patients was 153.7 mEq/L. DI mostly occurred within 1–3 days after surgery and lasted for 2–4 days. Moreover, 35 patients took desmopressin to control DI when they were discharged from the hospital; 33 were cured within 1–6 months of follow-up and 2 developed permanent DI. There were 219 patients (52.8%) who did not develop DI.

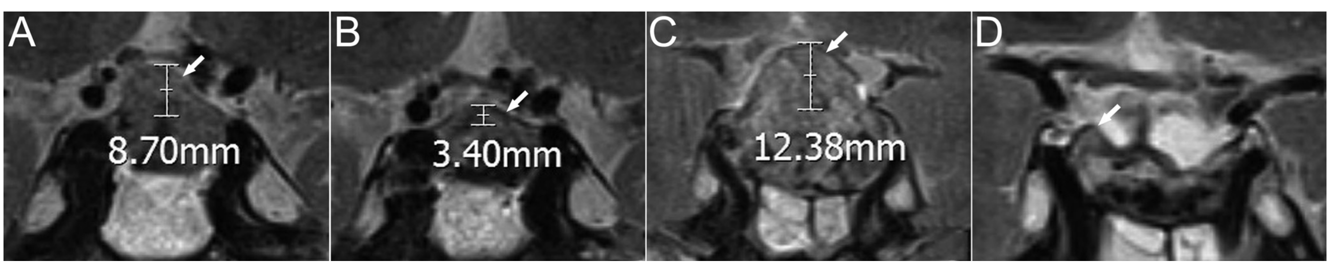

Figure 3
Magnetic resonance imaging reveals changes in the diaphragma sellae before and after transsphenoidal surgery in two cases. (A) and (B) correspond to one of the cases, and (C) and (D) to the other. Diaphragma sellae (arrow). (A) Hypointense shadow of the diaphragma sellae in preoperative T2-weighted imaging; diaphragma sellae height: 8.7 mm. (B) The sinking depth of the diaphragma sellae is the difference between the two values (8.7–3.4 mm). (C) Hypointense shadow of the diaphragma sellae in preoperative T2-weighted imaging; diaphragma sellae height: 12.38 mm. (D) The sinking depth of the diaphragma sellae is the difference between the two values (12.38–0 mm).

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Table 1 Demographic characteristics of 415 patients who underwent transsphenoidal surgery for pituitary adenomas.

Characteristics	No. (%)
Age, mean ± s.d. (years)	48.7 ± 13.3
Sex	
Men	216 (52.4)
Women	199 (47.6)
Tumor size, cm^3	5.64 ± 6.21
Tumor height, mm	23.07 ± 9.47
Tumor type	
Functioning pituitary adenomas	236 (56.9)
Non-functioning pituitary adenomas	179 (43.1)
Pathological type	
Gonadotropinoma	124 (29.9)
Null cell adenoma	105 (25.3)
Lactotroph adenomas	70 (16.8)
Somatotroph adenomas	36 (8.7)
Corticotroph adenomas	33 (8.0)
Plurihormonal adenomas	43 (10.3)
Thyrotroph adenomas	4 (1.0)
Intratumoral cysts or hematoma	
Yes	151 (36.4)
No	264 (63.6)
Location of PPBS	
Upper parts	181 (43.6)
Lower parts	179 (43.1)
Upper and lower parts	19 (4.6)
None	36 (8.7)
Invasiveness	
Yes	69 (16.6)
No	346 (83.4)

PPBS, posterior pituitary bright spot.

In the DI group, the average tumor volume was 3.9 cm^3; the average tumor height, 23.28 mm; and the occurrence of PPBS, 90.8%. There were 25 patients in the DI group who had invasion into the cavernous sinus; 34, intraoperative CSF leakage; and 167, total tumor resection. In the non-DI group, the average tumor volume was 3.6 cm^3; the average tumor height, 21.57 mm; and the occurrence of PPBS, 91.8%. There were 26 patients in the non-DI group who had invasion into the cavernous sinus; 35, intraoperative CSF leakage; and 186, total tumor resection (Table 2).

Factors influencing postoperative DI

Various factors between DI and non-DI groups were compared. Sinking depth of the DS was greater in patients with postoperative DI than in those without it ($P = 0.002$), as was a large pituitary stalk deviation angle difference ($P < 0.001$). No significant differences in age, sex, tumor volume, tumor height, intraoperative CSF leakage, and the degree of tumor resection were found between the DI and non-DI groups (Table 2).

Risk of postoperative DI

Based on the results of univariate analysis, we selected variables with P values < 0.05 for logistic regression analysis including the sinking depth of the DS and the pituitary stalk deviation angle difference. Logistic regression analysis showed that the risk of DI after TSS was higher in patients with a larger pituitary stalk deviation angle difference (odds ratio = 2.407, 95% CI = 1.335–4.342; $P = 0.004$) (Table 3). ROC analysis showed that the area under the ROC curve of the logistic regression model was 0.732 (Fig. 4).

Correlation between sinking depth of the DS and pituitary stalk deviation angle difference

We assessed the correlation between the sinking depth of the DS and the pituitary stalk deviation angle difference in all patients. Spearman's correlation analyses indicated a moderate positive correlation between these two factors ($r_s = 0.581$, $P < 0.001$).

Discussion

This is the first study to investigate the relationship between a change in pituitary stalk deviation angle, the sinking depth of the DS, and the occurrence of postoperative DI after TSS. We found that the pituitary stalk deviation angle difference was an independent predictor of postoperative DI. In addition, there was a moderate positive correlation between the sinking depth of the DS and the pituitary stalk deviation angle difference.

In this study, the incidence of DI was 47.2%, which is similar to that in the study of Oh *et al.* (7). However, previous studies reported differing predictive factors of DI after TSS. Nemergut *et al.* (8) showed that further operations were often required after pituitary microadenoma surgery to locate the lesion and that the posterior lobe of the pituitary was easily damaged; therefore, the risk of DI was higher after surgery. Nayak *et al.* (10) reported that a larger tumor volume tended to affect more structures around the tumor (especially the pituitary stalk) and that DI was more likely to occur after surgery. The results of the present study suggested that tumor size could not predict the occurrence of postoperative DI. It was also difficult to assess the level of destruction in the normal structures around the tumor when the tumor was removed during TSS.

Intraoperative CSF leakage occurs because of the excessive damage to the DS by surgical instruments during operation, which may also cause damage to the pituitary

Table 2 Univariate analysis of postoperative DI.

Factors	Postoperative DI (*n* = 196)	Non-postoperative DI (*n* = 219)	*P* value
Age	50 (41, 57)	49 (39, 61)	0.858
Sex			0.169
Men	109	107	
Women	87	112	
Tumor size, cm^3	3.9 (1.9, 7.6)	3.6 (1.8, 6.3)	0.266
Tumor height, mm	23.28 (16.39, 29.79)	21.57 (15.06, 28.20)	0.159
Tumor type			0.772
Functioning pituitary adenomas	110	126	
Non-functioning adenomas	86	93	
Pathological type			0.355
Gonadotropinoma adenomas	58	66	
Null cell adenomas	52	53	
Lactotroph adenomas	29	41	
Somatotroph adenomas	20	16	
Corticotroph adenomas	11	22	
Plurihormonal adenomas	23	20	
Thyrotroph adenomas	3	1	
Intratumoral cysts or hematoma			0.451
Yes	75	76	
No	121	143	
PPBS occurance			0.727
Positive	178	201	
Negative	18	18	
Invasiveness			0.784
Yes	25	26	
No	171	193	
The imaginary angle[a]	90.5 (75.2, 108.0)	96.0 (77.0, 123.0)	0.091
DS sinking depth	3.94 (0, 7.67)	1.54 (0, 5.61)	**0.002**
The pituitary stalk deviation angle difference (°)			**<0.001**
0 ≤ angle < 30	147	199	
30 ≤ angle < 60	46	19	
60 ≤ angle < 90	3	1	
Extent of tumor resection			0.503
Total resection	167	186	
Subtotal resection	12	9	
Partial resection	17	24	
Intraoperative CSF leakage			0.709
Yes	34	35	
No	162	184	

The pituitary stalk deviation angle difference: the difference between the preoperative and postoperative pituitary stalk deviation angle. Values are median (interquartile range).
CSF, cerebrospinal fluid; DI, diabetes insipidus; DS, diaphragma sellae; PPBS, posterior pituitary bright spot.
[a]The imaginary angle drawn between the two edges of DS begins its elevation and the highest point of the DS.

Table 3 Logistic regression analysis of the risk of postoperative DI onset.

Factors	OR	95% CI	*P* value
DS sinking depth	1.021	0.971, 1.074	0.415
The pituitary stalk deviation angle difference	2.407	1.335, 4.342	**0.004**

The pituitary stalk deviation angle difference: the difference between the preoperative and postoperative pituitary stalk deviation angle.
DI: diabetes insipidus; DS, diaphragma sellae; OR, odds ratio.

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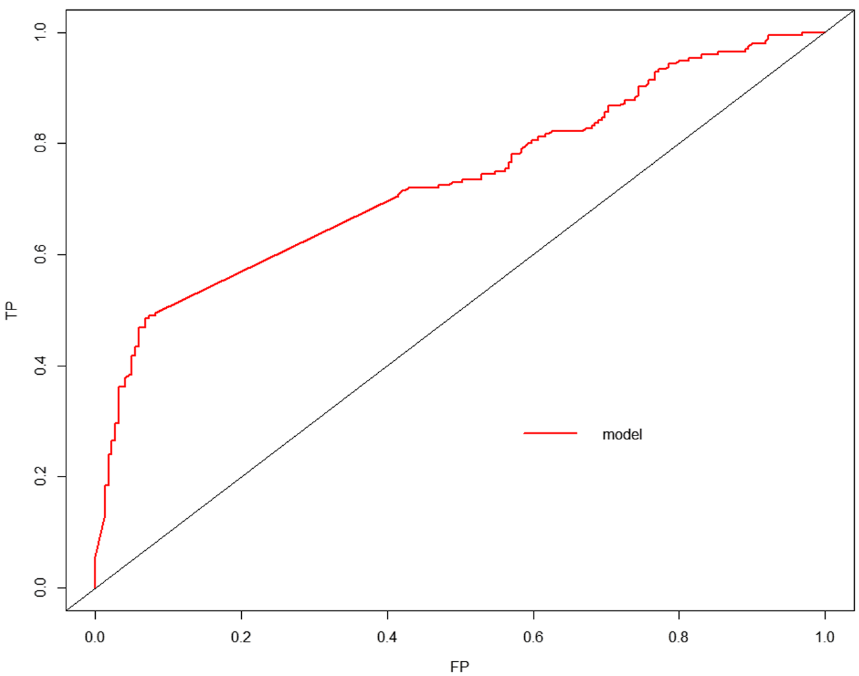

Figure 4
The validation of the logistic regression model showed that area under the receiver operating characteristic curves was 0.732.

stalk (4, 11). Nemergut *et al.* (8) reported that the use of a fat graft to seal the leak was accompanied by an inflammatory response, leading to the development of postoperative transient DI. However, the direct contribution of a fat graft to the development of DI still needs prospective validation. We did not find an association between intraoperative CSF leakage and the development of postoperative DI, which is consistent with the findings of Nayak *et al.* (10).

Araujo-Castro *et al.* observed that total tumor resection was related to an increased incidence of DI (4); they speculated that actively pursuing total tumor resection was likely to damage the remaining normal pituitary tissue or pituitary stalk, whereas conservative resection would retain a large amount of both tumor and pituitary tissues. However, Oh *et al.* argued that the degree of tumor resection was not correlated with postoperative DI (7).

In the present study, we judged cavernous sinus invasion using Knosp grade, which was not correlated with postoperative DI. Indeed, several studies have confirmed that cavernous sinus invasion is not different between patients with and without DI (7, 10). Suprasellar extension had a higher association with postoperative DI than cavernous sinus invasion did, and it affected the pituitary stalk with a high chance of ADH aberrations following surgery (10). Oh *et al.* showed that cephalocaudal tumor diameter could predict the occurrence of DI after TSS (7); they speculated that a large cephalocaudal tumor diameter would affect the release of diet-related hormones in the hypothalamus, leading to obesity and narrowing of the nasal cavity and increasing the difficulty of surgery, which in turn, would increase the risk of injury to the pituitary stalk and posterior pituitary lobe.

To summarize, different research centers have evaluated the relationship between tumor volume, tumor invasiveness, intraoperative CSF leakage, the degree of tumor resection, and postoperative DI from the perspective of surgical damage to the hypothalamic–neurohypophyseal system. However, these previous analyses were speculative.

The PPBS is well-characterized and thought to be the imaging correlate of membrane-bound secretory vesicles containing ADH in neurohypophysis (18). Saeki *et al.* (9) studied the relationship between the PPBS in 69 cases of PA and postoperative DI and found that patients had a higher risk of DI when they presented with negative PPBS. After further expanding the sample size in our study, we found that the visibility of PPBS could not predict postoperative DI. Preoperative DI is rare in patients with PA, and a nonvisible PPBS does not necessarily represent decompensation of the hypothalamus–neurohypophyseal system.

ADH, a neuropituitary hormone, is synthesized by large neurons in the supraoptic nuclei and paraventricular nucleus of the hypothalamus and is transported along the hypothalamic–pituitary tract to the posterior pituitary in the form of neurosecretory granules (5). When properly stimulated, these neurons become excited and transmit nerve impulses to the axon terminals in the neurohypophysis; as a result, the ADH and its carrier protein in the vesicle are released exocellularly into the blood (19). The secretion of ADH is mainly regulated by plasma osmotic pressure. Other factors such as circulating blood volume, exercise, and certain emotional states can also affect the release of ADH (8). After TSS, interruption of ADH delivery from the hypothalamus, alterations in the release of ADH from the posterior pituitary gland, or retrograde damage to the hypothalamic nucleus can lead to DI (8). Therefore, damage to any part of the hypothalamic–neurohypophyseal axis may lead to DI.

The results of univariate analysis showed that the sinking depth of the DS and the pituitary stalk deviation angle difference were greater in the DI group than in the non-DI group. The results of our multivariate analyses suggested that the pituitary stalk deviation angle difference was an independent predictor of the development of postoperative DI. The DS is a dural structure covering the upper surface of the adenohypophysis, and the pituitary stalk passes through the opening of the DS (20, 21). During the upward growth of the tumor, the DS is pushed up but can maintain its integrity (22, 23). The integrity of the DS is a prerequisite for sinking after TSS. Therefore, the DS sinks as the tumor is gradually removed during the operation. The position and shape of the pituitary stalk can change as the tumor grows (24); the pituitary stalk is chronically twisted, displaced, and even thinned. In the present study, we noted the display rate and location of the PPBSs and found a positive display rate of 91.3%; 181 of these were located in the upper part. This indicates that when pituitary tumors occur, transportation of ADH synthesized by the large neurons of the supraoptic nuclei and paraventricular nucleus of the hypothalamus to the posterior pituitary is blocked, thereby forming an ectopic posterior pituitary. The position of the PPBS can also help ascertain whether the pituitary stalk has undergone morphological changes.

From an anatomical viewpoint, not only the DS but also the arachnoid, tumor pseudocapsule, and flat pituitary tissue sink (20). Sinking of the DS affects the traction of the pituitary stalk, which further changes the position and shape of the pituitary stalk; this causes damage to the hypothalamic–neurohypophyseal tract and leads to the development of postoperative DI. In the present study, there was a moderate correlation between the sinking depth of the DS and the pituitary stalk deviation angle difference. Thus, sinking of the DS pulls the pituitary stalk down, which can cause DI after TSS for PA.

The DS sinking depth and the difference in the pituitary stalk deviation angle mentioned in this study can cue the surgeon as to how to best prevent the occurrence of postoperative DI. Particularly, during TSS, the DS above most tumors will gradually sink because of the pressure difference after tumor resection. To avoid or minimize this sinking, once the tumor has been resected, clinicians can perform intrasellar packing with gelatin sponges to restore the position of the DS to its maximum extent. This can prevent excessive sinking of the DS and mitigate stretching injury to the pituitary stalk, ultimately reducing the risk of developing postoperative DI. However, further research is needed.

In this study, only 8 patients (4%) had DI with transient hypernatremia. We believe that because patients undergoing TSS were conscious and had normal thirst regulation mechanisms, they were able to drink water independently, which allowed them to maintain normal or upper-range blood sodium levels.

Conclusion

The difference between the preoperative and postoperative pituitary stalk deviation angles was an independent predictor of the development of postoperative DI. Additionally, there was a moderate positive correlation between the sinking depth of the DS and the pituitary stalk deviation angle difference. Sinking of the DS can stretch the pituitary stalk, which in turn, can cause changes to its shape or position and damage to the hypothalamic–neurohypophyseal tract; this would contribute to disorders in the synthesis, transport, and secretion of ADH and ultimately lead to the development of DI.

Declaration of interest

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

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Ethics approval and consent to participate

Approval was obtained from the ethics committee of 900th Hospital. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all individuals participating in this study.

Data availability

The data sets generated and/or analysed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Author contribution statement

X L and W J W carried out the studies and drafted the manuscript. X L and C J participated in collecting data. X L performed the statistical analysis. Y Y K critically reviewed the manuscript. All authors read and approved the final manuscript.

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