Predictors of Postoperative Diabetes Insipidus Following Endoscopic Resection of Pituitary Adenomas

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Context: The development of diabetes insipidus (DI) following transsphenoidal resection of pituitary adenomas has been associated with higher postsurgical morbidity and longer hospitalizations. Identifying these patients promptly and efficiently can lead to improved health care outcomes.

Objective: We evaluated our institution's incidence of DI following pituitary adenoma resection and assessed for preoperative risk factors that were associated with postoperative DI.

Design: A retrospective review of 271 patients who underwent endoscopic endonasal resection of a pituitary adenoma between July 2010 and December 2016 by a single neurosurgical provider was completed.

Setting: All cases were from a single-center, academic institution.

Patients: Patients with a pituitary adenoma diagnosis confirmed on histology were included in the study. Those with previous surgery by a different provider were excluded.

Results: The incidence of DI at our institution was 16.6% (45 of 271 patients), with only 4% (11 patients) having permanent DI. The presence of visual abnormalities (CI 1.29 to 4.75), suprasellar extension (CI 1.36 to 6.88), and maximal tumor diameter (1.02 to 1.08) was significantly associated with an increased incidence of postoperative DI ($P < 0.05$). Hyperprolactinemia, tumor functionality, and cerebrospinal fluid exposure were not associated with higher rates of postoperative DI ($P > 0.05$).

Conclusion: Pituitary adenoma patients presenting with visual abnormalities, suprasellar extension, or large tumors are at higher risk of developing DI postoperatively. These patients warrant closer postoperative monitoring as well as adequate preoperative counseling to decrease their postsurgical morbidity.

Abbreviations: ADH, antidiuretic hormone; AVP, arginine vasopressin; CSF, cerebrospinal fluid; DI, diabetes insipidus; PRL, prolactin; RCC, Rathke cleft cyst; $S_{[Na]}$, serum sodium.

Preoperative diagnosis of diabetes insipidus (DI) is rare in the setting of a pituitary adenoma and should prompt consideration of alternative diagnoses, such as craniopharyngioma or Rathke cleft cyst (RCC) [1]. Postoperative DI, however, is not a rare finding after sellar mass resections, with reported incidences typically ranging from 9% to 22% but up to 54% at some institutions [1–10]. Although not all patients develop DI after transsphenoidal surgery, those that do typically require longer hospitalizations and face a higher morbidity [6]. Being able to avoid the adverse consequences from undiagnosed DI underscores the importance of correctly and efficiently identifying patients with DI following transsphenoidal surgery.

Unfortunately, the diagnosis of DI, especially in the hospitalized, postsurgical patient, is not always straightforward [1, 7]. The effects of anesthesia, postoperative complications, medications, nasal packing, and perioperative intravenous fluid use can contribute to a confusing diagnostic evaluation [1, 7]. An understanding of the postoperative antidiuretic hormone (ADH) pathophysiology and differential diagnoses of polyuria helps to clinically diagnose and test for DI. Following the diagnosis, close monitoring is required to evaluate treatment response and to determine whether the DI is transient, permanent, or part of the triphasic response [1, 7]. The majority of postoperative DI is transient, requiring treatment of 1 week (~50%) up to 3 months (~80%) [7]. Permanent DI is much less common, with a reported incidence of 2% to 7% [7]. The triphasic response is a postsurgical phenomenon that presents with a short period of DI, followed by the syndrome of inappropriate ADH secretion 5 to 7 days later, resulting in hyponatremia. Eventually, a proportion of these patients goes on to develop permanent DI. Although the full triphasic response is less common than permanent DI, with an incidence of 1.1%, managing these patients can be complicated and requires careful monitoring [1].

There have been studies that have retrospectively analyzed associations of preoperative and perioperative factors with DI that can be used to identify patients with a higher risk of developing postoperative DI. This could lead to closer postoperative monitoring of the high-risk population for a timely diagnosis and reduction in the postsurgical morbidity. Schreckinger *et al.* [6] evaluated 172 endoscopic transsphenoidal surgeries and determined tumor volume and histopathology of RCC or craniopharyngioma were associated with postoperative DI. They also reported that a postoperative serum sodium ($S_{[Na]}$) >145 mmol/mL or an increase of at least 2.5 mmol/L had 98% and 80% specificity, respectively, of developing DI [6]. An evaluation for the incidence of postoperative DI by Kadir *et al.* [2] at a single institution showed functioning pituitary adenomas (17.6%) were much less likely to be associated with DI than nonfunctioning pituitary adenomas (62.5%). A large, retrospective study of 881 patients by Nemergut *et al.* [4] showed an 18.3% incidence of postoperative DI, with 12.4% requiring treatment at some point during hospitalization and only 2% requiring long-term treatment. Their analysis of these patients showed an intraoperative cerebrospinal fluid (CSF) leak to be strongly associated with DI (33.3% transient and 4.4% permanent) [4]. Similar to the previous study, histopathology showing RCC or craniopharyngioma was associated with increased incidence of DI [4]. Corticotroph adenomas associated with Cushing disease had higher association with transient but not permanent DI [4]. Interestingly, repeat operations were not associated with higher incidence of DI and microadenomas were more likely to experience transient DI than macroadenomas [4].

The purpose of our study was to review our institution's experience with patients with pituitary adenoma following endoscopic endonasal resection to identify preoperative factors that were associated with the development of postoperative DI.

1. Materials and Methods

A. Study Subjects

After approval from The Ohio State University Institutional Review Board, an electronic query was performed to identify our sample of patients who had undergone transsphenoidal surgery. To remove surgical expertise as a variable, we limited the cases to those performed

by a single neurosurgeon (D.M.P.). We excluded diagnoses of RCC and craniopharyngioma, as these are known to carry a significantly higher risk of postoperative DI [4, 6]. Between August 2010 and December 2016, 314 patients were identified. Of these, 43 patients were excluded: 39 who had undergone a previous pituitary resection by a different provider or at a different institution, 2 with a histopathologic diagnosis of metastatic disease, and 2 with a preoperative diagnosis of DI. Two hundred seventy-one patients remained.

B. Data Collection

A retrospective chart review was completed on the 271 patients. Electronic medical records were reviewed to obtain demographic information, visual symptoms at presentation (subjective complaints confirmed by physician or objective report), anterior and posterior pituitary function at diagnosis, preoperative prolactin (PRL) level (if elevated), functional status of the tumor, maximal tumor diameter and tumor extension, tumor pathology, presence of intraoperative CSF exposure or leak, postoperative CSF leak, postoperative DI symptoms, diagnosis of DI, and/or treatment. For the measurement of the tumor size and extension, the data were collected from the original imaging reports. Due to the retrospective nature of the study, a single radiologist did not generate these reports. However, the data were assessed and confirmed by the neurosurgical team preoperatively.

C. Diagnostic Criteria

A standard institutional inpatient monitoring system was used in all postoperative patients regardless of symptoms, including hourly intake and output measurements for 48 hours. Urine osmolality, urine specific gravity, and $S_{[Na]}$ were tested every 6 hours for 48 hours after surgery. The monitoring was extended if there were abnormal findings. Specific criteria were used to confirm the diagnosis of DI for each patient: documentation of increased thirst and subjective polydipsia or polyuria or objective intake and output record showing >250 cc of urine output per hour for at least 2 hours along with a urine osmolality of <200 mOsm/kg and urine specific gravity <1.005 or an $S_{[Na]}$ >143 mmol/L. This standard postoperative monitoring and diagnostic criteria helped avoid missing those with DI who were well compensated by increasing their own intake without need for desmopressin treatment.

Once DI was confirmed, treatment methods were separated into four categories with the first three categories used in transient DI: symptomatic treatment that allowed patients to drink to thirst without desmopressin use, inpatient treatment with intermittent desmopressin use during hospitalization but discharge without medication, transient treatment requiring desmopressin at discharge but for <3 months from day of surgery, and permanent treatment requiring desmopressin for >3 months from surgery. Treatment of patients who experienced the triphasic response was classified per their final desmopressin status on last follow-up (i.e., inpatient, transient, or permanent requirement).

Patients with a clinical diagnosis of prolactinoma or positive PRL stain on histopathology were excluded only for the analysis of the association between hyperprolactinemia (due to stalk effect) with DI but not the remaining preoperative factors. If hyperprolactinemia was present based on the laboratory's age-specific and/or sex-specific PRL reference ranges, the level was recorded.

Tumor functionality and pituitary function were recorded when all appropriate laboratory evaluations or documentation were available. Tumor functionality was confirmed with postoperative histopathologic diagnosis, and the latter was documented separately for plurihormonal adenomas. Panhypopituitarism was defined as abnormalities in three or more of the hypothalamic-pituitary axes.

D. Statistical Analysis

The χ^2 and independent t tests were performed to compare data with categorical and continuous variables, respectively, on demographics between two groups (patients with

postoperative DI vs those without postoperative DI). The associations between risk factors and development of postoperative DI were analyzed using χ^2 and Fisher exact tests. Logistic regression was performed to analyze multiple predictors of development of postoperative DI. Differences on tumor size between groups were performed with independent t tests. P values were considered as significant at $P < 0.05$. Data were analyzed in SPSS V.23.0.

2. Results

Forty-five of 271 patients (16.6%) developed postoperative DI, whereas 226 patients (83.4%) did not. Demographically, the two groups did not significantly differ in age, sex, or race ($P > 0.05$) (Table 1). Of the 45 patients who developed DI, only 11 patients (4.0%) had permanent DI. Of the 34 patients (12.6%) with transient DI, 11 were monitored with symptomatic treatment, 8 required intermittent inpatient doses, and 15 required desmopressin at discharge but were able to wean off in <3 months. The average preoperative sodium level was not different between the two groups (DI group: average $S_{[Na]}$ 137.65 ± 2.15 mg/dL; patients with non-DI: average $S_{[Na]}$ 138.30 ± 2.53 mg/dL; $P = 0.15$).

With the implication that visual abnormalities involve some degree of optic chiasm disturbance, suprasellar extension, and stalk compression, we identified all patients who were diagnosed as having visual field deficits or visual acuity changes by a clinician. Expectedly, the presence of visual abnormalities at presentation was associated with a higher rate of DI postoperatively (48.9% vs 27.9%; $P = 0.006$) (Table 2).

To study the effect of pituitary dysfunction on DI, we separated panhypopituitarism and hyperprolactinemia, as anatomically these can lead to different postoperative pathology in relation to water and sodium balance [1]. However, neither diagnoses of panhypopituitarism nor hyperprolactinemia significantly predicted the incidence of postoperative DI in our study ($P > 0.05$) (Table 2). A further evaluation of average PRL levels in those with hyperprolactinemia between the two groups showed a PRL of 52.55 ng/mL in the DI group compared with 43.72 ng/mL in the non-DI group. Although there was a difference, this was not noteworthy.

With previous reports showing incongruent findings between functionality of tumors and DI [2, 4], we evaluated our institution's findings of the same. Of 271 patients, 178 had nonfunctioning pituitary adenomas, 34 had Cushing disease, 31 had acromegaly, 25 had prolactinomas, and 3 had TSH-omas. The incidence of each functional pituitary adenoma was not significantly different between those with DI and those without DI, and thus, functional tumors were not associated with postoperative DI ($P > 0.05$) (Table 1).

Table 1. Demographics and Adenoma Characteristics of Patients With and Without Postoperative DI

Variable	Postoperative DI (n = 45)	Non–postoperative DI (n = 226)
Age	53.40 ± 14.15	51.82 ± 16.75
Sex		
Male	24 (53.33)	109 (48.20)
Female	21 (46.67)	117 (51.80)
Race		
White	31 (68.90)	182 (80.50)
African American	10 (22.20)	33 (14.60)
Hispanic	3 (1.30)	3 (1.30)
Other	4 (8.90)	8 (3.60)
Clinical diagnosis		
Nonfunctioning	32 (71.11)	146 (64.60)
Cushing disease	5 (11.11)	29 (12.83)
Acromegaly	4 (8.89)	27 (11.95)
Prolactinoma	4 (8.89)	21 (9.29)
TSH-oma	0 (0.00)	3 (1.33)

Data are presented as n (%), or average ± SD.

Table 2. Associations Among Risk Factors and Postoperative DI (n = 271)

Variable	Postoperative DI (n = 45)	Non–postoperative DI (n = 226)	Odds Ratio of Development of Postoperative DI	95% CI	P Value
Visual abnormalities	48.90	27.90	2.48[a]	1.29–4.75	0.008
Panhypopituitarism	17.80	10.90	1.77	0.74–4.23	0.211
Hyperprolactinemia	23.1	28.20	0.77	0.34–1.73	0.691
Suprasellar extension	82.20	60.20	3.06[a]	1.36–6.88	0.006
Cavernous sinus extension	40.00	34.50	1.27	0.66–2.44	0.498
Other extension[b]	17.8	12.2	1.59	0.67–3.76	0.330
Intraoperative CSF exposure	48.90	36.7	1.65	0.87–3.14	0.135
Tumor maximal diameter	28.84 ± 15.93	21.52 ± 10.71	1.05[c]	1.02–1.08	0.000
Tumor size			2.55[a]	1.17–5.55	0.018
Microadenoma (<10 mm)	8.90	15.00			
Macroadenoma	75.60	80.50			
Giant adenoma (>40 mm)	15.60	4.40			

Data are presented as percentages or average unless otherwise noted.
[a]$P < 0.05$.
[b]Sphenoid sinus, clivus, or retrosellar.
[c]$P < 0.001$.

Radiologic findings have been previously evaluated using various strategies including tumor volume, anterior-posterior, cranio-caudal, or transverse dimensions and maximal tumor diameter, but findings have been inconsistent among studies [2, 4, 6, 11]. In our study, maximal tumor size significantly predicted higher risk of postoperative DI. The larger the adenoma, the higher the risk of postoperative DI ($P < 0.05$), with an average maximal tumor diameter of 28.8 mm in the DI group vs 21.5 mm in the non-DI group ($t = -3.01$; $P = 0.004$).

The effect of tumor extension, beyond Knosp grading or cavernous sinus invasion as previously studied, was evaluated by separating into three categories: suprasellar extension, cavernous sinus invasion, or other, involving retrosellar, clivus, or sphenoid sinus involvement. Only those patients with suprasellar extension had a higher association with postoperative DI (82.2% vs 60.2%; $P = 0.006$) (Table 2). Tumor extension in the remaining two categories was not significantly different between the two groups ($P > 0.05$) (Table 2).

A systematic review by Lobatto *et al.* [11] considered tumor size and suprasellar extension to be correlated. However, multivariate analysis of our data showed that tumor size was a significant predictor of postoperative DI independent of suprasellar extension ($P < 0.05$).

Lastly, we evaluated the association of either intraoperative CSF exposure or postoperative CSF leak with DI. Despite our nonsignificant results, there was a trend in the positive direction ($P = 0.069$) (Table 2).

When the significant predictors of visual abnormalities, suprasellar extension, and maximal tumor diameter were entered into the logistic regression model, only maximal tumor diameter significantly predicted postoperative DI ($P < 0.05$).

To address confounding factors in our data, we examined two additional variables: diuretic use and postoperative hyperglycemia. For this analysis, we studied all 45 patients with DI and a random sample of 60 patients without DI from the cohort. We found that the rate of diuretic use was not significantly different in the two populations, and in fact, there were more patients on diuretics in the non-DI group (DI group: 17.8%; non-DI group: 31.7%; $P = 0.25$). To assess the role of hyperglycemia in postoperative polyuria, we examined maximum the incidence of hyperglycemia greater than the renal threshold of 180 mg/dL between the two groups also showed no significant differences (DI: 12 out of 45; non-DI: 9 out of 60; $P = 0.109$). In addition, we recorded the maximal blood glucose obtained within the 48-hour postoperative period, and this also showed no differences between the groups (DI: 158.5 ± 52.51 mg/dL; non-DI: 154.7 ± 45.42 mg/dL; $P = 0.348$).

Additionally, we evaluated whether any of the aforementioned factors were associated with increased risk of permanent DI over transient DI. When the analyses were performed on the 45 patients who developed postoperative DI, only maximal tumor diameter was found to have a significantly higher association with permanent DI [n = 11; X = 38.91 mm, (X = average ± SD)] vs transient DI (n = 34; X = 25.59 mm) ($P < 0.05$). All other preoperative factors were not significant ($P > 0.05$) (Table 3).

3. Discussion

In the evaluation of our institution's experience with DI following pituitary adenoma resection, we assessed the association of several preoperative factors with DI to assist in the postoperative diagnosis and management as well as patient education. Our retrospective review of 271 patients with pituitary adenomas shed light on additional factors that are more likely to predict DI and also reiterated the importance of tumor size, as seen in some previous studies [4, 11]. Although 16.6% of patients developed DI postoperatively, the rate of permanent DI was much lower at 4%, consistent with the incidence reported at other institutions [1, 2, 4, 7–10, 12].

The presence of visual abnormalities, either visual field deficits and/or acuity changes, was significantly associated with postoperative DI. A total of 25.9% of patients with visual symptoms went on to develop postoperative DI, whereas only 12.4% of those without visual symptoms developed DI. Visual abnormalities typically indicate tumor compression of the optic nerve or chiasm. With the anatomic location of the optic chiasm being superior to the pituitary gland, we would expect the presence of upward extension of the tumor to involve the pituitary stalk as well. During surgical manipulation, this disturbance of the pituitary stalk could result in disruption of arginine vasopressin (AVP) release and thus DI.

In our group, tumor size was a notable predictor of postoperative DI, consistent with previous studies' findings with tumor volume and diameter [4, 11]. This is likely due to the higher chance of involvement of nearby structures, specifically the pituitary stalk, with larger tumors. Overall, there was a significant skew toward larger tumors in the DI group ($P < 0.001$). We observed that 15.60% of patients with DI had giant adenomas (>40 mm in maximal dimension) compared with only 4.40% in the non-DI group. Clinically, this is relevant, as patients with giant adenomas were 2.5 times more likely to develop DI than those with microadenomas and warrant closer DI monitoring postoperatively.

Table 3. Associations Among Risk Factors and Transient vs Permanent DI (n = 45)

Variable	Permanent Postoperative DI (n = 11)	Transient Postoperative DI (n = 34)	Odds Ratio of Development of Postoperative DI	95% CI	P Value
Visual abnormalities	63.60	44.10	2.27	0.55–9.01	0.314
Panhypopituitarism	18.20	17.60	1.04	0.18–6.08	0.968
Hyperprolactinemia	36.40	17.90	2.63	0.55–12.55	0.238
Suprasellar extension	90.90	79.40	2.59	0.28–23.80	0.657
Cavernous sinus extension	27.30	44.10	0.48	0.11–2.11	0.482
Other extension[a]	11.80	36.40	4.29	0.86–21.48	0.085
Intraoperative CSF exposure	63.60	44.10	2.22	0.55–9.01	0.314
Tumor maximal diameter	38.91 ± 17.89	25.59 ± 13.51	1.06[b]	1.01–1.12	0.023
Tumor size			3.25	0.74–14.21	0.118
Microadenoma (<10 mm)	0.00	11.80			
Macroadenoma	72.70	76.50			
Giant adenoma (>40 mm)	27.30	11.80			

Data are presented as percentages or average unless otherwise noted.
[a]Sphenoid sinus, clivus, or retrosellar.
[b]$P < 0.05$.

Previous studies have looked for association with higher Knosp grading or cavernous sinus extension with DI with neutral results [11, 12]. By dividing tumor extension into three groups—suprasellar extension, cavernous sinus extension, and other extension including the sphenoid sinus, clivus, or retrosellar—we were able to identify substantial differences. Suprasellar extension affects the pituitary stalk with a higher chance of causing AVP disturbance following surgical manipulation. As expected, a higher rate of suprasellar extension was seen in the DI group (82.2% vs 60%). This is important in preoperative counseling and planning, as only 8.2% of patients without suprasellar extension developed DI, whereas 21.4% (37 of 173 patients) with suprasellar extension developed DI. Involvement of the cavernous sinus or other areas indicates lateral or anterior-posterior extension with less chance of pituitary stalk disturbance, and accordingly, a noteworthy difference was not identified.

Multivariable analyses of the 173 patients with suprasellar extension showed a notable difference in maximal tumor diameter in those who developed DI (average dimension of 32.43 mm) compared with those who did not (25.05 mm). Thus, tumor size remained a noteworthy predictor of DI independent of the presence of suprasellar extension.

Contrary to our expectations, hyperprolactinemia was not associated with higher DI risk. Albeit not statistically significant, the analysis of the absolute PRL levels in those with hyperprolactinemia showed the group that developed DI had an average PRL of 52.55 ng/mL compared with 43.72 ng/mL in those that did not develop DI ($P > 0.05$). Pathophysiologically, an elevated PRL indicates stalk effect with tumor involvement of the pituitary stalk [13]. Similar to variability seen with TSH levels [14–16], two studies have revealed the presence of both interindividual and intraindividual PRL variation, with the former having a larger variation [17, 18]. This variation could explain the nonsignificant findings in our analysis.

The presence of panhypopituitarism was not associated with higher DI risk in our group. The incidence of panhypopituitarism following resection of pituitary adenomas ranges between 5% and 25% and has been associated with larger tumors, extent of surgical manipulation, recurrent disease, and Cushing disease [7]. Given that size of tumor is a noteworthy predictor for both panhypopituitarism and DI, a correlation might have been expected between the two. However, the pituitary gland can often remain functional despite considerable mass effect from large tumors. Additionally, when the pituitary-adrenal axis is compromised, DI can be masked due to the lack of the normal glucocorticoid inhibition of ADH synthesis and release. With initiation of glucocorticoid replacement, symptoms of polyuria and polydipsia can present, revealing DI. This highlights the importance of a complete pituitary evaluation preoperatively and postoperatively and helps in the differential diagnosis for polyuria.

Few studies have shown a higher incidence of postoperative DI with Cushing disease [4, 7]. In our group, this was not the case, as the rate of Cushing disease, acromegaly, prolactinomas, and nonfunctional adenomas did not differ significantly between the two groups (Table 1). In addition, there was no substantial association with transient over permanent DI in those with Cushing disease as previously described [4] (Table 4). It has not been clearly established why certain functioning tumors would have a higher risk of DI. Nemergut *et al.* [4] suggested a more extensive explorative surgery or glycosuria yielding higher rates of polyuria in Cushing disease. Other studies indicate that functional tumors typically present as larger and more aggressive tumors, leading to higher incidence of DI, as seen with acromegaly [19, 20]. In addition, the postsurgical diuresis that patients with acromegaly experience could be mistaken for DI, leading to inappropriate diagnosis [1]. However, in our group, only 4 of the 31 patients with acromegaly met diagnostic criteria for DI, which was similar to other functional and nonfunctional adenomas.

In evaluating preoperative factors associated with the development of permanent vs transient DI, our data showed maximal tumor diameter to be the only noteworthy predictor of postoperative DI. Unfortunately, due to our overall low numbers of permanent DI (11 patients), the analysis lacked power to identify differences between the remaining factors. To be able to study this further would likely require a meta-analysis given the overall low incidence of permanent DI at most high-volume, experienced pituitary surgery centers [4, 6, 9–12].

Table 4. Demographics and Adenoma Characteristics of Transient vs Permanent DI

Variable	Transient DI (n = 34)	Permanent DI (n = 11)
Age	52.71 ± 13.99	55.55 ± 15.11
Sex		
Male	14 (41.18)	8 (72.73)
Female	20 (58.82)	3 (27.27)
Race		
White	23 (67.65)	8 (72.73)
African American	8 (23.53)	2 (18.18)
Hispanic	3 (8.82)	0 (0.00)
Other	0 (0.00)	1 (9.09)
Clinical diagnosis		
Nonfunctioning	22 (64.71)	10 (90.90)
Cushing disease	5 (14.71)	0 (0.00)
Acromegaly	3 (8.82)	1 (9.10)
Prolactinoma	4 (11.76)	0 (0.00)
TSH-oma	0 (0.00)	0 (0.00)

Data are presented as n (%), or average ± SD.

The strengths of our study are the size of our study sample, the single-center and single-surgeon data used to evaluate for noteworthy predictors, as well as our exclusion criteria to include only pituitary adenomas. Limiting to a single neurosurgical provider removes the substantial variability that surgical experience could have on the development of DI. In addition, to our knowledge, our study was the only one to limit evaluation to pituitary adenomas. We elected to use this limitation as the incidence of DI with craniopharyngiomas and RCC has consistently been reported to be significantly higher (31% to 50%) than in pituitary adenomas [4, 11]. These above exclusions strengthen the impact of our findings for pituitary adenomas.

The limitation of our study is the retrospective nature that can restrict data collection. The diagnosis of DI required clear subjective documentation, objective findings, and laboratory evaluation and treatment with desmopressin. Despite the standard protocol for every postoperative patient, transient DI could have been missed in those patients with intact thirst mechanisms and access to water that self-regulated their treatment. Also, given the retrospective nature, a single laboratory was not used to evaluate hypothalamic pituitary axes in all patients preoperatively. Data were collected as available through various providers' notes and not included in analyses if incomplete. Finally, we were limited by the fact the MRIs were not evaluated by a single radiologist, thus precluding centralized review and uniform size measurements for tumors; this concern is mitigated by the fact that the neurosurgeon (D.M.P.) reviewed all scans preoperatively.

It is worth mentioning the exciting literature emerging regarding the use of copeptin, an amino acid fragment of the pro-AVP polypeptide that is cosecreted with AVP [21]. Serum copeptin levels have shown promising results in their ability to differentiate primary polydipsia from central or nephrogenic DI with adequate sensitivity and specificity [21–23]. However, the reference range in various settings that stimulate AVP release, such as nausea, vomiting, pain, or stress, has yet to be established. This analyte may prove to be a great tool in the future once the initial findings are confirmed and the test becomes more available in the clinical setting.

4. Conclusion

Because the diagnosis and treatment of postoperative DI can be complex, using preoperative data to identify those at highest risk can be meaningful to patient care and outcomes. Our comprehensive review of pituitary adenoma data from one surgical provider at our institution highlights several preoperative factors that were associated with higher incidence of

postoperative DI. Although all postoperative patients require monitoring for DI, patients presenting with vision changes, suprasellar extension, or large tumors on MRI were found to have a higher incidence of DI. This group should be counseled appropriately preoperatively and monitored closer postoperatively. These associated factors can be anatomically explained with their effect on the pituitary stalk, where AVP traverses en route to the posterior pituitary. Due to the overall low incidence of permanent DI, meta-analysis of high-volume institutions' experience would be clinically helpful in gaining insight into predictors of permanent DI beyond tumor size.

Acknowledgments

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References and Notes

1. Devin JK. Hypopituitarism and central diabetes insipidus: perioperative diagnosis and management. *Neurosurg Clin N Am*. 2012;**23**(4):679–689.
2. Kadir ML, Islam MT, Hossain MM, Sultana S, Nasrin R, Hossain MM. Incidence of diabetes insipidus in postoperative period among the patients undergoing pituitary tumour surgery. *Mymensingh Med J*. 2017;**26**(3):642–649.
3. Kiran Z, Sheikh A, Momin SN, Majeed I, Awan S, Rashid O, Islam N. Sodium and water imbalance after sellar, suprasellar, and parasellar surgery. *Endocr Pract*. 2017;**23**(3):309–317.
4. Nemergut EC, Zuo Z, Jane JA Jr, Laws ER Jr. Predictors of diabetes insipidus after transsphenoidal surgery: a review of 881 patients. *J Neurosurg*. 2005;**103**(3):448–454.
5. Qari FA, AbuDaood EA, Nasser TA. Diabetes insipidus following neurosurgery at a university hospital in Western Saudi Arabia. *Saudi Med J*. 2016;**37**(2):156–160.
6. Schreckinger M, Walker B, Knepper J, Hornyak M, Hong D, Kim JM, Folbe A, Guthikonda M, Mittal S, Szerlip NJ. Post-operative diabetes insipidus after endoscopic transsphenoidal surgery. *Pituitary*. 2013;**16**(4):445–451.
7. Prete A, Corsello SM, Salvatori R. Current best practice in the management of patients after pituitary surgery. *Ther Adv Endocrinol Metab*. 2017;**8**(3):33–48.
8. Constantino ER, Leal R, Ferreira CC, Acioly MA, Landeiro JA. Surgical outcomes of the endoscopic endonasal transsphenoidal approach for large and giant pituitary adenomas: institutional experience with special attention to approach-related complications. *Arq Neuropsiquiatr*. 2016;**74**(5):388–395.
9. Kim JH, Lee JH, Lee JH, Hong AR, Kim YJ, Kim YH. Endoscopic transsphenoidal surgery outcomes in 331 nonfunctioning pituitary adenoma cases after a single surgeon learning curve. *World Neurosurg*. 2018;**109**:e409–e416.
10. Zhan R, Ma Z, Wang D, Li X. Pure endoscopic endonasal transsphenoidal approach for nonfunctioning pituitary adenomas in the elderly: surgical outcomes and complications in 158 patients. *World Neurosurg*. 2015;**84**(6):1572–1578.
11. Lobatto DJ, de Vries F, Zamanipoor Najafabadi AH, Pereira AM, Peul WC, Vliet Vlieland TPM, Biermasz NR, van Furth WR. Preoperative risk factors for postoperative complications in endoscopic pituitary surgery: a systematic review. *Pituitary*. 2018;**21**(1):84–97.
12. Jang JH, Kim KH, Lee YM, Kim JS, Kim YZ. Surgical results of pure endoscopic endonasal transsphenoidal surgery for 331 pituitary adenomas: a 15-year experience from a single institution. *World Neurosurg*. 2016;**96**:545–555.
13. Kadashev BA, Konovalov AN, Astaf'eva LI, et al. Preoperative and postoperative endocrine disorders associated with pituitary stalk injuries caused by suprasellar growing tumors. *Vopr Neirokhir*. 2018;**82**(1):13–21.
14. Maes M, Mommen K, Hendrickx D, Peeters D, D'Hondt P, Ranjan R, De Meyer F, Scharpé S. Components of biological variation, including seasonality, in blood concentrations of TSH, TT3, FT4, PRL, cortisol and testosterone in healthy volunteers. *Clin Endocrinol (Oxf)*. 1997;**46**(5):587–598.

15. Meier CA, Maisey MN, Lowry A, Müller J, Smith MA. Interindividual differences in the pituitary-thyroid axis influence the interpretation of thyroid function tests. *Clin Endocrinol (Oxf)*. 1993;**39**(1): 101–107.

16. Hoermann R, Midgley JE. TSH measurement and its implications for personalised clinical decision-making. *J Thyroid Res*. 2012;**2012**:438037.

17. Partsch CJ, Lerchl A, Sippell WG. Characteristics of pulsatile and circadian prolactin release and its variability in men. *Exp Clin Endocrinol Diabetes*. 1995;**103**(1):33–43.

18. Cohen MR. Prolactin studies in normals: implications for clinical research. *Psychiatry Res*. 1983;**8**(4): 299–310.

19. Sarkar S, Rajaratnam S, Chacko G, Chacko AG. Endocrinological outcomes following endoscopic and microscopic transsphenoidal surgery in 113 patients with acromegaly. *Clin Neurol Neurosurg*. 2014; **126**:190–195.

20. Starnoni D, Daniel RT, Marino L, Pitteloud N, Levivier M, Messerer M. Surgical treatment of acromegaly according to the 2010 remission criteria: systematic review and meta-analysis. *Acta Neurochir (Wien)*. 2016;**158**(11):2109–2121.

21. Christ-Crain M, Morgenthaler NG, Fenske W. Copeptin as a biomarker and a diagnostic tool in the evaluation of patients with polyuria-polydipsia and hyponatremia. *Best Pract Res Clin Endocrinol Metab*. 2016;**30**(2):235–247.

22. Winzeler B, Zweifel C, Nigro N, Arici B, Bally M, Schuetz P, Blum CA, Kelly C, Berkmann S, Huber A, Gentili F, Zadeh G, Landolt H, Mariani L, Müller B, Christ-Crain M. Postoperative copeptin concentration predicts diabetes insipidus after pituitary surgery. *J Clin Endocrinol Metab*. 2015;**100**(6): 2275–2282.

23. Timper K, Fenske W, Kühn F, Frech N, Arici B, Rutishauser J, Kopp P, Allolio B, Stettler C, Müller B, Katan M, Christ-Crain M. Diagnostic accuracy of copeptin in the differential diagnosis of the polyuria-polydipsia syndrome: a prospective multicenter study. *J Clin Endocrinol Metab*. 2015;**100**(6): 2268–2274.