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Authors

Ajlan, Abdulrazag M
Abdulqader, Sarah Bin
Achrol, Achal S
et al.

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Diabetes Insipidus following Endoscopic Transsphenoidal Surgery for Pituitary Adenoma

Abdulrazag M. Ajlan[1,2] Sarah Bin Abdulqader[3] Achal S. Achrol[1] Yousef Aljamaan[4] Abdullah H. Feroze[1] Laurence Katznelson[1,5] Griffith R. Harsh[1]

[1] Department of Neurosurgery, Stanford University, Palo Alto, California, United States
[2] Department of Neurosurgery, King Saud University, Riyadh, Saudi Arabia
[3] College of Medicine, King Saud University, Riyadh, Saudi Arabia
[4] College of Medicine, University of Dammam, Dammam, Saudi Arabia
[5] Department of Medicine, Stanford University, Palo Alto, California, United States

Address for correspondence Abdulrazag M. Ajlan, MD, FRCSC, Department of Neurosurgery, Stanford University, Palo Alto, CA, United States (e-mail: aajlan@stanford.edu).

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Abstract

Objectives Pituitary adenoma (PA), among the most commonly encountered sellar pathologies, accounts for 10% of primary intracranial tumors. The reported incidence of postoperative diabetes insipidus (DI) is highly variable. In this study, we report our experience with DI following endoscopic transsphenoidal surgery (TSS) for PAs, elucidating the risk factors of postoperative DI, the likelihood of long-term DI, and the impact of DI on the length of stay (LOS).

Methods The study included 178 patients who underwent endoscopic resection of PAs. Early DI was defined as that occurring within the first postoperative week. The mean follow-up was 36 months. Long-term DI was considered as DI apparent in the last follow-up visit.

Results Of the 178 patients included in the study, 77% of the tumors were macroadenomas. Forty-seven patients (26%) developed early DI. Long-term DI was observed in 18 (10.1%) of the full cohort. Age younger than 50 years was significantly associated with a higher incidence of long-term DI ($p = 0.02$). Macroadenoma and gross total resection were significantly associated with higher incidence of early DI ($p = 0.05$ and $p = 0.04$, respectively). The mean LOS was 4 days for patients with early postoperative DI and 3 days for those without it.

Conclusion The reported incidence of postoperative DI is significantly variable. We identified age younger than 50 years a risk factor for developing long-term postoperative DI. Gross total surgical resection and tumor size (> 1 cm) were associated with development of early DI. Early DI increased the LOS on average by 1 day.

Keywords
- diabetes insipidus
- endoscopic transsphenoidal
- pituitary adenoma
- postoperative hypernatremia

Introduction

Pituitary adenoma (PA), among the most commonly encountered sellar pathologies, accounts for 10% of primary intracranial tumors.[1] Transsphenoidal surgery (TSS) became the preferred treatment for most adenomas in the 1960s. Over the last two decades, many surgeons have shifted from the microscope to the endoscope for TSS[2,3] in the hope that its superior visualization would result in fewer complications.

Numerous series have reported the frequencies of various complications of endoscopic TSS.[1,2,4–7] The reported incidence of postoperative diabetes insipidus (DI) is highly

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variable, ranging from 0.3 to 45%,[8–18] perhaps reflecting inconsistent definition, varying interval of follow-up, and diverse sellar pathologies.

Although DI can usually be managed successfully, it may lead to serious complications, including dehydration and seizures.[8] It is the second most common cause of unplanned readmission following TSS,[19] and its occurrence prolongs hospital stay an additional 4 to 7 days.[4]

In this study, we report our experience with DI following endoscopic resection of PAs, elucidating the risk factors of postoperative DI, the likelihood of long-term DI, and the impact of DI on the length of hospital stay.

Methods

We conducted a retrospective chart review of patients who underwent endoscopic resection of PAs between 2007 and 2012 at the Stanford University. The project was approved by the Institutional Review Board.

The study included 183 patients operated on by the senior author (G.R.H.). Five patients were excluded because of missing DI follow-up data, resulting in 178 patients for further analysis.

The diagnosis of DI was made based on polyuria, $>$ 300 mL/h for 3 consecutive hours, urine-specific gravity $<$ 1.005, and plasma sodium $>$ 145 mmol/L. Early DI, usually apparent during the surgical admission, was defined as that occurring within the first postoperative week. We evaluated patients at 1, 2 weeks, 3, 6 months, 1 year, and then yearly after surgery. The mean follow-up was 36 months (range: 1–78 months). Patients were considered to have long-term DI based on symptoms of polydipsia and polyuria and the criteria above at the last follow-up visit (mean 36 months).

Univariate logistic regression was used to analyze risk factors relating to DI including age, gender, tumor size, adenoma type, previous surgery, gross total resection, cerebrospinal fluid (CSF) leak, and early DI. Tumor type and natremic status were screened individually for each versus all others.

Results

Of the 178 patients included in the study, 84 (47%) were male and 94 (53%) were female. The mean age was 50 years (range: 18–89). Sixty-seven (37%) patients presented with hormonal disturbance and 49 (27%) presented with headache (►**Table 1**). Seventy-seven percent of the tumors were macroadenomas. Gross total resection was achieved in 136 (67%) tumors.

Forty-seven patients (26%) developed early DI; of these, 12 (26%) had DI on long-term follow-up and 35 (74%) did not. Of the 131 who did not have early DI, 6 (4.6%) developed long-term DI and 125 (95.4%) did not. Long-term DI was observed in 18 (10.1%) of the full cohort (►**Fig. 1**).

From the full cohort, 23 patients were on steroids preoperatively (4 cases for mass effect and 19 cases for preoperative adrenal axis insufficiency). In addition, we had 11 cases of Cushing's disease that were discharged on steroids. Moreover, in the last follow-up visit, 48 patients were on steroids for treatment of long-term adrenal axis insufficiency. However, the relation among preoperative steroids use, postoperative steroids use on discharge, and long-term steroids use with long-term DI did not reach statistical significance ($p = 0.887$, $p = 0.442$, and $p = 0.443$, respectively).

Age younger than 50 years was significantly associated with a higher incidence of long-term DI (odds ratio [OR] = 0.03; 95% confidence interval [CI]: 0.09–0.9; $p = 0.02$) but not early DI (OR = 0.7; 95% CI: 0.3–1.3; $p = 0.2$). Macroadenoma and gross total resection were significantly associated with higher incidence of early DI (OR = 2.5; 95% CI: 1.0–6.4; $p = 0.05$ and OR = 2.6 95%; CI: 1.0–6.6; $p = 0.04$, respectively). Neither tumor type nor previous surgery was identified as a risk factor for early DI or long-term DI (►**Tables 2–4**).

Intraoperative CSF leak was a risk factor for both early DI (OR = 6.2; 95% CI: 1.5–26.1; $p = 0.005$) and long-term DI (OR = 7.1; 95% CI: 2.5–20.4; $p < 0.0001$). Early DI was strongly prognostic for long-term DI (OR = 7.1; 95% CI: 2.5–20.4; $p < 0.0001$) (►**Table 4**).

The mean length of stay (LOS) was 4 days (median: 4 days, range: 1–15 days, $p = 0.01$) for patients with early postoperative DI and 3 days (median: 2 days, range: 1–18 days) for those without it (►**Fig. 2**).

Table 1 Patients' characteristics

Total number of patients	178
Median age, y (range)	50 (18–89)
	N (%)
Sex	
Male	84 (47)
Female	94 (53)
Presenting symptoms	
Hormonal disturbance	67 (37)
Headache	49 (27)
Vision impairment	33 (18)
Incidental	23 (13)
Apoplexy	11 (6)
Other	8 (4)

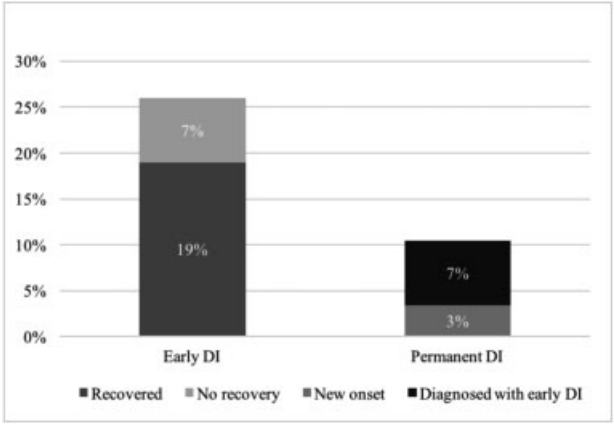

Fig. 1 Incidence of diabetes insipidus (DI).

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Table 2 Incidence of DI based on tumor types and size

	Total	Early DI			Permanent DI		
	N (%)	*N* (%)	OR (95% CI)	*p*–Value	*N* (%)	OR (95% CI)	*p*-Value
Tumor type							
Nonfunctional	108 (61)	32 (30)	1.5 (0.8–3.1)	0.2	14 (13)	2.5 (0.8–7.8)	0.1
Prolactin secreting	27 (15)	8 (30)	1.2 (0.5–3.0)	0.7	3 (11)	1.1 (0.3–4.2)	0.8
GH secreting	25 (14)	4 (15)	0.5 (0.1–1.5)	0.2	0 (0)	–	0.07
ACTH secreting	16 (9)	2 (13)	0.4 (0.1–1.7)	0.2	1 (6)	0.6 (0.07–4.6)	0.6
TSH secreting	2 (1)	1 (50)	2.8 (0.2–46.1)	0.5	0 (0)	–	0.6
Tumor size							
Microadenoma	41 (23)	6 (15)	2.5 (1.0–6.4)	0.05	3 (7)	1.6 (0.4–5.7)	0.5
Macroadenoma	137 (77)	41 (30)	–	–	15 (11)	–	–

Abbreviations: ACTH, adrenocorticotropic hormone; CI, confidence interval; DI, diabetes insipidus; GH, growth hormone; OR, odds ratio; TSH, thyroid-stimulating hormone.

Table 3 Incidence of DI based on preoperative patients' characteristics

	Total	Early DI			Permanent DI		
	N (%)	*N* (%)	OR (95% CI)	*p*-Value	*N* (%)	OR (95% CI)	*p*-Value
Age (y)							
Younger than 50	93 (52)	28 (30)	0.7 (0.3–1.3)	0.2	14 (15)	0.3 (0.09–0.9)	0.02
Older than 50	85 (48)	19 (22)	–	–	34 (5)	–	–
Sex							
Male	84 (47)	22 (26)	1.0 (0.5–1.9)	0.9	9 (11)	1.1 (0.4–3.0)	0.8
Female	94 (53)	25 (27)	–	–	9 (10)	–	–
Previous surgery							
Yes	22 (12)	4 (18)	0.6 (0.2–1.8)	0.4	1 (5)	0.4 (0.05–3.1)	0.4
No	156 (88)	43 (28)	–	–	17 (11)	–	–

Abbreviations: CI, confidence interval; DI, diabetes insipidus; OR, odds ratio.

Table 4 Incidence of DI based on intraoperative and postoperative patients' characteristics

	Total	Early DI			Permanent DI		
	N (%)	*N* (%)	OR (95% CI)	*p*-Value	*N* (%)	OR (95% CI)	*p*-Value
Resection							
Gross total	136 (76)	41 (30)	2.6 (1.0–6.6)	0.04	14 (10)	1.1 (0.3–3.5)	0.9
Subtotal	42 (24)	6 (14)	–	–	4 (10)	–	–
Intraoperative CSF leak							
Yes	52 (29)	22 (26)	1.2 (0.6–2.5)	0.6	10 (19)	3.5 (1.3–9.5)	0.01
No	126 (71)	25 (27)	–	–	8 (6)	–	–
Postoperative CSF leak							
Yes	9 (5)	6 (66)	6.2 (1.5–26.1)	0.005	2 (22)	2.7 (0.5–14.3)	0.2
No	169 (95)	41 (24)	–	–	16 (10)	–	–
Early DI							
Yes	47 (26)	–	–	–	12 (30)	7.1 (2.5–20.4)	< 0.0001
No	131 (74)	–	–	–	6 (4)	–	–

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; DI, diabetes insipidus; OR, odds ratio.

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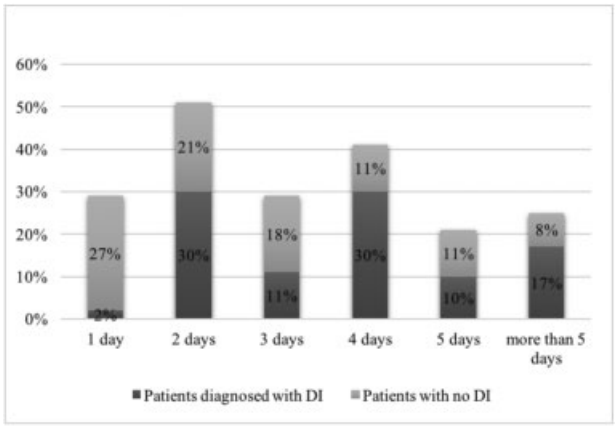

Fig. 2 Length of hospital stay.

Discussion

Although reports suggest that endoscopic surgery has similar or superior outcomes with respect to DI than does microsurgery,[20,21] the risk of DI after endoscopic TSS is still significant, ranging from 0.3 to 10%[8–14] for permanent and 1.6 to 45%[9,11,12,15–18] for transient DI. In this study, the incidences of early DI and long-term DI were 26 and 10%, respectively.

Gondim et al[14] reported a similar incidence (10%) of permanent DI. That study hypothesized that their relatively high incidence reflected the giant size of tumors in the study (all $>$ 4 cm in largest diameter) and the resulting risk of hypothalamic injury from suprasellar dissection.[14]

A large series of 1,571 microscopically resected PAs showed a higher incidence of transient DI (35%) diagnosed on the basis of 24-hour urine output more than 2,500 mL and specific gravity less than 1.005 g/L.[10] Sigounas et al,[9] evaluating DI in endoscopically resected tumors found a low incidence of both transient (13.6%) and permanent (2.7%) DI. They included nonneoplastic and congenital lesions in their study. Their criteria for diagnosis included urine-specific gravity less than 1.004 and urine output more than 300 mL/h for 3 consecutive hours. Transient DI was defined as DI lasting for less than 6 months.[9]

A recent review of DI after TSS for various sellar pathologies approached by different techniques reported an incidence of transient and permanent DI to be 29 and 1.8%, respectively, for a sublabial and transspetal approaches, 25 and 2%, respectively, for a microscopic transnasal approach, and 5 and 1.5%, respectively, for an endoscopic transnasal approach.[22]

A meta-analysis of 11 studies directly comparing microscopic and endoscopic surgeries found an overall incidence of DI of 15% in the endoscopic group and 28% in the microscopic group ($p = 0.003$).[21] A different meta-analysis comparing endoscopic and sublabial approaches found an incidence of permanent DI of 2% with endoscopy and 3% with sublabial microscopy ($p = 0.1$).[20] In addition, in a recent meta-analysis of 23 studies comparing endoscopic resection of PA to microscopic resection (2,272 patients), they reported 22% reduction in the rate of DI using the endoscope, but this difference did not reach statistical significance.[23] This concludes that endoscopic surgery predominates microscopic surgery in terms of reducing the risk of DI.

In our endoscopic series, the incidence of long-term DI was 10.1%. This relatively high rate may reflect our diagnostic criteria, the tumors' size (77% were macroadenomas), and their hormonal type (39% were endrochronological active). In this study, we did not compare the rate of DI between the endoscopic and microscopic groups. However, in an analysis of Patil et al[24] that was coauthored by the senior author (G.R.H.) which evaluated multiple outcomes of microscopic TSS for Cushing's disease from 1993 to 2002 on a national level, the risk of DI was 15%. This rate most likely represents early DI as their data were obtained from inpatient database and did not include any follow-up data. Moreover, in a previous analysis by the first author (A.M.A.) comparing the endoscopic and microscopic approaches, there was no significant variation in the rate of DI between the two groups.[25] This might be reflected by the relatively small sample in that study.

We identified age younger than 50 years and intraoperative CSF leak as risk factors for developing long-term postoperative DI. Although young age has been previously reported as a risk factor for permanent DI,[10,26] Kristof et al[26] suggest that young age is not an independent risk factor for electrolyte imbalance, as patients with hormone-producing PAs are generally known to be younger than patients with hormone inactive PAs. Our series included 70 (39%) functional tumors, of which four patients (three with prolactin-secreting tumors and one with an ACTH-secreting tumor) were diagnosed with permanent DI (►**Table 2**).

In our study, the risks of early DI and long-term DI in nonfunctional PAs were 30 and 13%, respectively; this did not reach statistical significance compared with those for other PA subtypes. Our results concur with those of Schreckinger et al[11] who found that none of the adenoma subtypes was predictive of postoperative DI. Moreover, in a study evaluating outcomes following endoscopic resection of 26 growth hormone-secreting tumors, only two patients were diagnosed with transient DI and no cases of permanent DI were detected.[6] On the contrary, patients with Cushing's disease might be at increased risk of developing permanent DI.[10] This was not observed in our series, which could be related to a less aggressive surgical resection suggested by a relatively low rate of hormonal remission in our cases of Cushing's disease of 64%.

In our series, tumor diameter more than 1 cm (macroadenoma) and gross total resection were associated with higher incidence of early DI but not long-term DI. Both factors were previously reported as a risk factor for developing postoperative DI.[11,13] In our series, 77% of the tumors were macroadenomas and gross total resection was achieved in 67% of tumors. In theory, attempting total resection of large tumors could lead to more manipulation of the pituitary gland, pituitary stalk, and its vascular supply. However, small size (microadenoma) also has been reported to be a risk factor for DI.[10,15] Interestingly, neither factor was associated with higher incidence of long-term DI in our series.

The presence of CSF leak either intraoperatively or postoperatively carries a higher risk for developing DI. In the this

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study, 19% ($p = 0.01$) of patients who had intraoperative CSF leak developed long-term DI and 66% ($p = 0.005$) of those with postoperative leak were diagnosed with early DI. The risk of DI following endoscopic surgery increases from 21 to 37% in the presence of intraoperative leak.[9] Even with microscopic surgery, the risk of postoperative DI increases from 11 to 33% if intraoperative CSF leak is observed.[15] Intraoperative or postoperative CSF leak likely reflects not just suprasellar extension but also more ambitious resection of tumor that carries greater risk to the posterior lobe and pituitary stalk. Furthermore, we did not include the grading of the CSF leaks and their repair in our analysis. This signifies the potential effect of some techniques in preventing DI. In our cases, when intraoperative CSF leak is evident or suspected, this is generally managed with lumbar drainage, fat graft, fascia late, and solid reconstruction.

The mean length of hospital stay in our series was 3.3 days, similar to the LOS in a recent meta-analysis (mean 3.3).[20] The mean LOS for patients diagnosed with DI was 4 days in our study.

Most reported cases of postoperative DI are transient, manifesting within 24 to 48 hours of surgery and resolving within 3 to 5 days postoperatively.[9,27] Sodium level $>$ 145 mmol/L in the first 5 days postoperatively has been suggested to predict permanent DI.[9] Thomas et al[28] described a protocol seeking a short hospital stay in which discharge began on postoperative day 1. Patients were educated on the signs and symptoms of DI and were followed by daily phone calls for at least 4 days after discharge; 92% of patients were discharged on postoperative day 1 (mean stay of 1.16 days). Using this protocol, the diagnosis of early DI was not associated with an increase in LOS. Since DI can be readily detected and managed on an outpatient basis without increase in morbidity, for patients without imbalance of intake and output or abnormal serum sodium levels, the simple possibility of developing DI does not warrant longer postoperative stays, but patients with younger age, a larger tumor, intraoperative CSF leak, and postoperative hypernatremia, all risk factors for postoperative DI, warrant close monitoring.[10,11,15,26]

The reported incidence of postoperative DI is significantly variable. We identified age younger than 50 years and intraoperative CSF leak as risk factors for developing long-term postoperative DI. Gross total surgical resection and tumor size ($>$ 1 cm) were associated with development of early DI. Two-thirds of patients who developed early DI did not have long-term DI. Early DI increased the LOS on average by 1 day but did not change the overall LOS in our series. The concern of DI should not delay discharge from the hospital.

Conflict of Interest
None.

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