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Diabetes Insipidus after Endoscopic Endonasal Pituitary Macroadenoma Resection: Correlation of Patient and Surgery-Related Risk Factors

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Abstract

Purpose This article aims to identify patient- and surgery-related factors that could predict the development of postoperative central diabetes insipidus (DI).

Methods This is a retrospective case–control study conducted at a single-institution tertiary referral center. Patients undergoing endoscopic endonasal skull base surgery for pituitary adenoma between November 2018 and April 2023 were recruited. The main outcome measures collected include age, gender, comorbidities, tumor type, postoperative DI, intraoperative and postoperative cerebrospinal fluid (CSF) leak, flow of CSF leak, number of layers required for repair, the use of nasal packing, and hospital length of stay.

Results A total of 20 patients developed DI postoperatively. Patients' demographic and comorbidity profile did not correlate with DI development. The encounter of an intraoperative CSF leak was correlated with postop DI (chi-square (1) = 18.35, $p < 0.001$) with a relative risk (RR) of 2.7 (confidence interval [CI] = 1.37–5.28). The use of nasal packs was also correlated with postop DI (chi-square (1) = 10.17, $p = 0.001$) with a RR of 1.8 (CI = 1.15–2.87). Defects requiring a two or more layers for reconstruction also correlated with postop DI compared to single layer repairs (chi-square (1) = 12.15, $p < 0.001$) irrelevant of the materials used. Development of DI postop correlated with an increased hospital length of stay ($t(64) = -3.35$, $p = 0.001$).

Conclusion The physician should be careful when evaluating patients with pituitary adenomas in the postoperative period, particularly those with intraoperative CSF leak, nasal packing, and those who underwent multilayer reconstruction of the surgical defect.

Keywords
- diabetes insipidus
- endoscopic surgery
- skull base surgery
- pituitary adenoma

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Introduction

The endoscopic approach to pituitary surgery offers several advantages over the traditional microsurgical approach primarily attributed to the endoscope itself, which provides a superior close-up view of relevant anatomy, an expanded working angle, and an increased panoramic vision within the surgical area. Outcomes in terms of mass removal, alleviation of clinical symptoms, resolution of underlying diseases, and complication rates are comparable, if not superior, to major microsurgical series. This led to the adoption of endoscopy in transsphenoidal surgery as the mainstay approach for pituitary tumors.[1] When used to treat pituitary adenomas, endoscopic endonasal skull base surgery is associated with an average overall complication rate of 12.3%, the most common complication being wound infection (10.3%) followed by cerebrospinal fluid (CSF) leak/meningitis (7.5%). Vascular injuries and endocrine dysfunction such as diabetes insipidus (DI) have only been reported in 4% of patients.[2]

Central DI (CDI) is defined as absent or minimal vasopressin secretion due to damage to the hypothalamus or posterior pituitary gland. In most cases, this pathology is acquired from iatrogenic injuries, such as surgery and trauma.[3] From the patient's perspective, CDI has a major impact on patient well-being with 64% of patients reporting a decrease in quality of life and 36% reporting psychological changes.[4]

The prevalence of DI following endoscopic endonasal pituitary surgery (EEPS) for pituitary adenoma has been widely investigated with highly variable results. Some reviews found its prevalence to be as low as 4%,[2,5] while other studies reported values between 20 and 30%.[6,7] Understanding the factors that can predict the development of CDI postoperatively is of paramount importance to initiate early therapy and minimize the impact on the patient's quality of life. Factors such as age, size of the tumor, and location of the tumor have been previously investigated.[6,7]

The objective of this study is to add to the literature by identifying patient- and surgery-related factors that could predict the development of postoperative CDI.

Materials and Methods

After having obtained institutional review board approval (IRB ID: BIO-2023-0194), the medical records of patients undergoing endoscopic endonasal skull base surgery between November 2018 and April 2023 were retrospectively reviewed. A total of 103 cases were initially identified, 66 of which were diagnosed with pituitary adenomas and thus were included in this study. Intraoperative lumbar drain was used in all cases to help with surgical exposure and decrease intracranial pressure by continuous drainage. It was kept postoperatively in 17 patients when extensive dissection and reconstruction was done, especially in cases of large macroadenomas.

The diagnosis of postoperative CDI was based on three main parameters: increased urine output ($>$ 300 mL/h for 3 hours), increased serum sodium level ($>$ 145 mEq/L), and decreased urine specific gravity ($<$ 1.005). Among patients diagnosed with postoperative CDI, all were found to have a transient disease defined as signs and symptoms of DI (mainly polydipsia and polyuria) that resolved within 12 months following the surgery.[8]

The following data were collected from the patient's chart: age, gender, comorbidities (diabetes, hypertension, dyslipidemia, and others), tumor type and size, extrasellar extension, intraoperative and postoperative CSF leak, flow of CSF leak (high vs. low), intraoperative repair of defect, number of layers required for repair, the use of nasal packing, and hospital length of stay (LOS). Tumors exceeding 10 mm in size were defined as macroadenomas and those smaller than 10 mm were considered as microadenomas.

Surgical Technique

All surgeries were performed by a neurosurgeon in collaboration with an otolaryngologist. In select cases, the abdomen and thigh were prepped for possible fat and fascia lata harvest. Access to the tumor was achieved by the otolaryngologist where the bilateral sphenoid ostia were identified and opened giving access to the sphenoid sinuses and sellar floor. Then, the neurosurgeon removed and expanded the bony floor of the sella using a Kerrison rongeur. The dura was identified and opened in a door trap fashion. Upon opening, the thin pituitary gland layer was exposed and cut in a trap door fashion as well, then dissected where a clear plane was identified. Using ring curette the lesion was smoothly dissected in all directions. A four-hand technique was adopted providing continuous exposure using the scope. Total gross resection of the tumor was achieved. When a CSF leak was encountered, a nasoseptal flap was then designed for reconstruction of the sellar defect. Small defects were reconstructed either with Surgicel and glue alone or with fascia lata and a layer of overlying glue. Large defects required a vascularized fat. In these cases, the fascia lata and periumbilical fat were plugged in using a nasoseptal flap in a gasket seal fashion. In this case, a Merocel pack is used to hold the repair in place.

It is worth noting that multilayer reconstruction (three layers) was mainly used for high-flow leaks, whereas smaller leaks were managed by either one or two layered reconstruction. Almost all materials used for repair were autologous (nasoseptal flap, fascia lata, and abdominal fat) with Surgicel and glue being complementary synthetic materials. Merocel packing was only used whenever the patient needed CSF leak repair.

Statistical Analysis

All statistical analyses were performed using Statistical Analysis Package for Social Sciences (SPSS, version 29.0 Chicago, Illinois, United States). Descriptive statistics were used to compute the means and the standard deviation of the continuous variables and the frequencies of the categorical variables. The median values were compared using the Mann–Whitney *U* test, Fisher's exact test, and the chi-squared test with 95% confidence intervals (CIs). The logistic regression model was used to calculate the relative risks (RRs) with 95% CIs for the risks of postoperative DI. Multivariate analysis was performed to account for the effect of

intraoperative factors on DI. *p*-Values less than 0.05 were considered statistically significant.

Results

Patient and Surgery Characteristics

A total of 66 patients with pituitary adenomas who underwent EEPS were included in this study. The female-to-male ratio was 1.44 and the average age of the study population was 45 ± 17.7 years. Less than half of the patients were smokers (47%) and less than one-fourth had medical comorbidities such as hypertension (27.3%), diabetes mellitus (18.2%), dyslipidemia (13.6%), and coronary artery disease (10.6%). In 42 cases, the pituitary adenoma was identified as nonsecreting in nature (63.6%). Seventeen patients (25.8%) presented for revision pituitary surgery. Navigation was used in 8 of the 66 patients (12.1%). Lumbar drains were inserted intraoperatively in all patients and were kept postoperatively in 17 patients (25.8%). CSF leak was encountered intraoperatively in 19 cases (28.8%) and postoperatively in only 3 (4.5%). Twenty-six defects required closure/intervention, 19 of which were for CSF leak. Nasal packing was used in 24 (36.4%) patients. The mean length of hospital stay was 2.85 ± 1.55 days (►**Table 1**).

Risk Factors Correlating with Diabetes Insipidus after EEPS

A total of 20 patients developed DI following surgery (30.3%) and all were found to have transient DI. Patients' gender, tumor pathology, tumor size, and extrasellar extension did not correlate with the occurrence of DI ($p = 0.322$; $p = 0.560$; $p = 0.630$; $p = 0.095$). The encounter of a CSF leak intraoperatively was correlated with postoperative DI (chi-square $(1) = 18.35$, $p < 0.001$) with a RR of 2.7 (CI = 1.37–5.28). Moreover, patients with high-flow CSF ($n = 11$) were more likely to develop postoperative DI (72.7%) compared to patients with low-flow CSF ($n = 8$; 62.5%) and those with no CSF leak (14.9%) ($p < 0.001$). The use of nasal packs was also correlated with postop DI (chi-square $(1) = 10.17$, $p = 0.001$) with a RR of 1.8 (CI = 1.15–2.87). Defects requiring two or more layers for reconstruction also correlated with postop DI compared to single layer repairs (chi-square $(1) = 12.15$, $p = 0.001$) with a RR of 2.4 (CI = 1.16–4.99) irrelevant of the materials used. A multivariate analysis revealed a significant effect of intraoperative leak ($F = 24.66$, $p < 0.001$, $\eta^2 = 0.278$), high-flow leak ($F = 23.1$, $p < 0.001$, $\eta^2 = 0.265$), and nasal packing ($F = 11.66$, $p = 0.001$, $\eta^2 = 0.154$) on the prevalence of postoperative DI. The occurrence of DI following surgery significantly increased hospital LOS to 3.75 ± 1.55 days compared to 2.46 ± 1.39 days for patients who did not develop DI ($t(64) = -3.35$, $p = 0.001$) (►**Tables 2** and **3**).

Table 1 Demographic characteristics of the study population

Demographic data ($N = 66$)	Value
Gender (female/male ratio)	1.44
Age in years (mean ± SD)	45 ± 17.7
Smoking, *n* (%)	31 (47)
Comorbidities, *n* (%)	
Hypertension	18 (27.3)
Diabetes mellitus	12 (18.2)
Dyslipidemia	9 (13.6)
Coronary artery disease	7 (10.6)
Type of adenoma, *n* (%)	
Nonsecreting	42 (63.6)
GH-secreting	10 (15.2)
Cushing's	7 (10.6)
Prolactinoma	7 (10.6)
Type of surgery, *n* (%)	
Primary	49 (74.2)
Revision	17 (25.8)
Hospital LOS in days (mean ± SD)	2.85 ± 1.55

Abbreviations: GH, growth hormone; LOS, length of stay; SD, standard deviation.

Table 2 Factors associated with the development of postoperative diabetes insipidus

Factors, *n* (%)	DI ($n = 20$)	No DI ($n = 46$)	*p*-Value
Intraoperative CSF leak	13 (65)	6 (13)	< 0.001[a]
Nasal packing	13 (65)	11 (23.9)	0.001[a]
Multilayer reconstruction	12 (60)	6 (13)	0.001[a]

Abbreviations: CSF, cerebrospinal fluid; DI, diabetes insipidus.
[a]Statistically significant.

Discussion

Predicting the development of CDI following EEPS in patients with pituitary adenoma is a topic that gained increasing interests from otolaryngologists and neurosurgeons. Although the management is primarily based on adequate hydration and desmopressin administration, identifying patient-related and surgery-related risk factors as predictors of postoperative DI is of paramount importance in surgical planning and in initiating early treatment strategies. The main risk factors investigated in the literature are the age of the patient, size of the tumor, tumor histology,

Table 3 Relative risk of factors to develop postoperative diabetes insipidus

		95% confidence interval	
Features	RR	Lower	Upper
Intraoperative CSF leak	2.7	1.37	5.28
Nasal packing	1.8	1.15	2.87
Multilayer reconstruction	2.4	1.16	4.99

Abbreviations: CSF, cerebrospinal fluid; RR, relative risk.

intraoperative CSF leak, gross total resection, postoperative serum copeptin levels, and pituitary stalk stretch, among others. Additional features that may be of value include the rate of CSF flow, the use of nasal packing postoperatively, and the number of layers used for repair of defects during the surgery.

The results of this investigation revealed that patients with intraoperative CSF leak had 2.7 times greater risk of developing postoperative CDI, especially those with high-flow leaks. The use of nasal packs and defects requiring two or more layers for reconstruction were also predictors of postoperative CDI with RRs of 1.8 and 2.4, respectively. Other risk factors such as patient's age, comorbidities, and tumor characteristics did not correlate with CDI.

Our findings are in agreement with many studies in the literature on the predictive factors of postoperative DI in patients with pituitary adenomas who had undergone endoscopic endonasal transsphenoidal surgery. In 2005, Nemergut et al investigated the patient- and surgery-specific risk factors for DI in 881 patients who had undergone transsphenoidal microsurgery and noted that patients with intraoperative CSF leak (33.3%), those with Cushing's disease (22.2%), and those with microadenomas (21.6%) had an increased risk of transient DI following surgery.[9] In 2008, Sigounas et al studied 119 consecutive patients undergoing endoscopic pituitary surgery and noted that intraoperative CSF leak (36.8%) and previous nonendoscopic transsphenoidal pituitary surgery (42.9%) were associated with the development of postoperative DI, in contrast to other factors such as adenoma size and type.[10] In 2022, Tanji et al conducted a retrospective study on 101 patients with pituitary adenoma who underwent EEPS to evaluate the effect of intraoperative CSF leak, as classified by the Esposito grade, on the occurrence of DI after surgery. Interestingly, the authors noted that the odds of having DI postoperatively increased from 2.65 to 6.51 as the size of the leak increased from a grade 1 Esposito to a grade 3.[11] One likely explanation of the mechanism by which intraoperative CSF leak may predispose to DI lies in the extent of resection and pituitary stalk manipulation. In fact, CSF leak arises from iatrogenic damage to the diaphragm, the posterior lobe of the pituitary, or its stalk, subsequently resulting in DI.

When looking at the role of nasal packs in triggering DI, it is hypothesized that nasal packing triggers a local foreign body inflammatory reaction in the postoperative period, inciting the development of CDI. Merocel tampons induce histopathological changes in the nasal mucosa characterized by degeneration and dysplastic changes in epithelial cells in addition to inflammation and mucosal edema in the subepithelium within 24 hours of insertion.[12] Moreover, inflammation is a well-known etiology of CDI as Hayashi et al found in their study on six patients with Rathke cleft cyst. The authors discussed that the mechanism behind delayed DI occurrence can be attributed to the spreading of inflammatory chemicals from the cyst content into the area of the pituitary gland.[13]

The number of layers used when repairing surgical defects is also thought to contribute to the pathogenesis of postoperative DI. In 2020, Khatiwala et al retrospectively reviewed the charts of 38 patients with intraoperative high-flow CSF leak repair during EEPS using fascia lata button graft and nasoseptal flap. Among the minor postoperative complications encountered in this study, DI occurred in 13.16% of patients.[14] In another study on 101 patients evaluating the impact of multilayer reconstruction after endoscopic skull base surgery, Simal-Julián et al reported 7 cases of postoperative DI. The surgical technique, which was applied on 32 patients with nonadenomatous sellar pathologies, involved a layer of intradural fat, an epidural layer of fascia lata, and a final layer of vascularized flap.[15] The rationale behind the recipient-site complications depends on the type of layer used. Autologous fat grafts may induce central nervous system (CNS) complications due to fat necrosis and dissemination of fat into the subarachnoid space.[16] Early and late CNS complications have also been associated with fascia lata grafts perhaps because of the difficult manipulation during reconstruction.[17] If the nasoseptal flap is used, displacement or partial dehiscence of the flap's rim increase the tension on the flap and result in incomplete coverage with subsequent flap failure and irritation to the local mucosa.[18] It is also important to mention that nasal packs and multilayer reconstructions are employed in cases where extensive surgical work has been done. They are often used when a high-flow leak is encountered after significant surgical manipulation. These factors alone predispose to the development of DI and might be a confounding factor in our results. More studies are needed to pinpoint the etiology of DI in these patients, and differentiate between iatrogenic, inflammatory, and postsurgical etiologies.

The importance of identifying those risk factors lies in reducing the hospital LOS of operated patients with pituitary adenomas. The increased LOS of patients with postoperative DI in this study corroborates the findings of Benjamin et al in 2022, who aimed to design a protocol for evaluating, diagnosing, and treating postoperative endocrinopathy following resection of pituitary adenomas. Among the 171 patients included in the study, 31 developed DI and received desmopressin, which increased the LOS to 7.39 days in comparison to 4.36 days for the remaining 140 patients ($p < 0.0001$).[19]

The results of this investigation highlight the role of patient- and surgery-related factors, namely, intraoperative CSF leak, nasal packing, and multilayered reconstruction in predicting the development of CDI following EEPS. Nevertheless, this study has its limitations. One is its retrospective nature and the limited sample size. Second, the authors did not evaluate other risk factors such as the tumor size and endocrine parameters such as postoperative serum copeptin levels, which could play a substantial role in predicting CDI in patients undergoing endoscopic pituitary surgery.

Conclusion

Patient- and surgery-related factors have a great value in identifying patients at risk of developing postoperative DI following endoscopic endonasal surgery for pituitary adenomas. The physician should be vigilant when evaluating patients with pituitary adenomas in the postoperative period, particularly those with intraoperative CSF leak, nasal packing,

and those who underwent multilayer reconstruction of the surgical defect. This aims to individualize treatment strategies and decrease the hospital LOS of admitted patients.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Informed Consent

Due to the retrospective nature of the study, the rights to obtain informed consent were waived.

Conflict of Interest

None declared.

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