

Predictors of Cerebrospinal Fluid Leaks in Endoscopic Surgery for Pituitary Tumors

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Abstract: *Background:* Cerebrospinal fluid (CSF) leak is a serious complication of endoscopic endonasal surgery for pituitary adenoma; leading to a more serious and financial burden of the surgery. Prediction of the occurrence of such sequelae and proper planning for reconstruction can reduce its prevalence and associated morbidities. *Purpose:* To determine the predictors and risk factors associated with intra/and postoperative cerebrospinal fluid (CSF) leaks in endoscopic endonasal pituitary surgery. *Methods:* A retrospective study included 150 patients who underwent endoscopic endonasal approach for resection of pituitary adenomas between 2015 and 2018. We analyzed the association between CSF leaks (intra/post-operative) and perioperative variables including patients' demographic data, medical comorbidities, tumor characteristics and operative data (rates of intraoperative leak, reconstructive techniques). *Results:* 34 patients (22.6%) out of the 150 patients had an overall CSF leak: 26 (76.5%) patients had intraoperative leaks; 5 patients out of them continued to have a postoperative leak. 8 patients (23.5%) had postoperative leak. Based on multiple logistic regression model analysis; increased body mass index (BMI), associated hydrocephalus, suprasellar extension and recurrent tumors had a significant association with intraoperative CSF leaks, while only BMI and hydrocephalus predicted postoperative CSF leaks. *Conclusion:* Elevated BMI, suprasellar extension of the tumor, recurrence or previous radiation are all important risk factors that have been proved in this study to have statistically significant association with the incidence of CSF leak. In high risk patients for CSF leakage: adequate reconstruction plans advised to avoid such morbidity.

Keywords: CSF, Leak, Endoscopic Endonasal, Pituitary Surgery, Predictors

1. Introduction

Endoscopic endonasal skull base surgery has become widely implemented to be the gold standard in surgical treatment of pituitary tumors that have an estimated prevalence of 15%. Endoscopic endonasal approaches (EEA) has superior efficacy compared with microscopic approaches, as it provides enhanced visualization of the surgical field and decrease the incidence rate of postoperative cerebrospinal fluid (CSF) leaks and allow for proper management of such problem if occurred [1, 2, 5].

Unfortunately, CSF leaks remain one of the most prevalent

complications in endoscopic skull base surgery in the literature. Different cohort studies reported rates of CSF leak ranging between 2% and 64% [1, 17]. Intraoperative leaks are more common (14.2%-61%) than postoperative leaks (1.3%-16.7%), and many patients experiencing postoperative leaks have an observed intraoperative leak [6]. CSF leakage pathogenesis is explained by arachnoid violation during tumor resection. CSF leaks after endoscopic skull base surgery can lead to meningitis, subsequent prolonged morbidity, longer hospitalization time and further financial burden [18].

Identification of preoperative risk factors can guide the

preoperative planning for intraoperative CSF leakage reconstruction procedure from the start to achieve low morbidity rate especially in patients at increased risk [15].

Many reports in the literature had studied the impact of different risk factors included: patient and tumor variables; age, race, gender, and body mass index (BMI). Tumor size, extension and histopathological diagnosis; with variable outcomes [8]. There were no solid conclusions in published case series to predict the intraoperative and postoperative CSF leakage.

The aim of our study was to present our experience of endoscopic endonasal skull base surgery to identify the predictors associated with intra- and postoperative CSF leaks after an endoscopic endonasal approach (EEA) for resection of pituitary tumors; that could potentially change perioperative management.

2. Patients and Methods

This is a retrospective cohort study conducted at our skull base unit, Neurosurgery Department, Mansoura University Hospitals. Institutional Review Board approval was obtained to perform a retrospective review of patients who underwent endoscopic skull base surgery between June 2015 and December 2018. 150 cases diagnosed with pituitary adenomas were involved in the study. All patients were operated upon via endoscopic transsphenoid approach by the skull base team (neurosurgeons and otolaryngologist). All the patient's medical records were collected. Patient's demographic data, relevant medical information, imaging studies, laboratory studies, anesthetic records, operative records and postoperative data were collected and analyzed. All data regarding previous treatment of the adenomas whether surgical or previous radiation therapy were collected and assessed for its relevance. All patients underwent preoperative radiological evaluation (1.5 tesla MRI brain, sellar views, CT scan of brain and paranasal sinuses with thin slice skull base cuts). Collected MRI finding included; tumor size (maximal tumor diameter), hydrocephalus, pituitary apoplexy, suprasellar extension, associated empty sellae and

cavernous sinus invasion. Laboratory data for pituitary function were collected for identification the nature of adenoma. Operative data collected included the technique of endoscopic approach whether monostril or binostril technique, occurrence of intraoperative CSF leak, the usage of intraoperative lumbar drain and reconstruction methods used for repair. All patients were admitted to ICU overnight of surgery for monitoring and observation. All data of postoperative sequelae were reviewed including CSF rhinorrhea, diabetes insipidus (DI), intracranial infection, and pneumocephalus.

Statistical Analysis

Data was analyzed using (SPSS) Statistical Package for Social Sciences version 20. Categorical variables are presented as absolute number and frequency (%), and continuous variables are presented as mean \pm standard deviation (SD), range, or median with interquartile range (IQR) in text and tables. All continuous variables were assessed for normality using the Kolmogorov-Smirnov test. If these variables were not normally distributed, descriptive measurements such as median and IQR were calculated. Comparisons of patient characteristics were performed using a Chi-square test or Fisher's exact test for categorical variables in cases with a small number of expected outcomes. All independent variables thought to be of clinical significance were placed into a logistic multiple regression model. A p value of <0.05 was considered to indicate a statistically significant difference for all statistical tests.

3. Results

A total of 150 endonasal endoscopic transsphenoidal surgeries that met our inclusion criteria. The average age of patients at surgery was 41.82 ± 5.22 years ranged from 21 to 65 years. With a relatively equal distribution of females ($n=83$, 55.4%) and males ($n=67$, 44.6%). Among those 150 cases; 34 cases (22.6%) had intraoperative and post-operative CSF leakage. Patients' demographic data, associated medical comorbidities, previous treatment and tumor criteria are summarized in table 1.

Table 1. Perioperative univariate variable analysis of factors affecting incidence of overall CSF leak.

Variable	Mean \pm SD or (n,%)			P value
	All (n=150)	CSF leak (N=34)	No CSF leak (N=116)	
Age (years)	41.82 \pm 5.22	42.43 \pm 6.51	41.29 \pm 4.48	.500
Gender (male)	67 (44.6%)	44%	44.8%	.629
BMI (kg/m ²)	32.4 \pm 1.97	35.5 \pm 2.53	29.56 \pm 1.58	<.001
Hypertension	55(36.6%)	16 (47%)	39 (33.6%)	.423
Empty sellae	2 (1.3%)	1 (2.9%)	1 (0.8%)	.168
Preoperative radiation	4 (2.6%)	2 (5.8%)	2 (1.6%)	.001
Recurrence	16 (10.6%)	8 (23.5%)	8 (6.8%)	<.001
Pituitary apoplexy	13 (8.6%)	4 (11.6%)	9 (7.7%)	.054
Hydrocephalus	6 (4%)	4 (11.6%)	2 (1.6%)	.001
Mean tumor size	3.6 \pm 1.2	3.1 \pm 1.14	2.7 \pm 0.9	.002
Suprasellar	40 (26.5%)	17 (50%)	23 (19.8%)	<0.001
Cavernous sinus	46 (30.6%)	13 (38.2%)	33 (28.4%)	.002
Diabetes insipidus	6 (4%)	4 (11.7%)	2 (1.7%)	.030
Intracranial infection	3 (2%)	2 (5.8%)	1 (0.8%)	.692

Variable	Mean±SD or (n,%)			P value
	All (n=150)	CSF leak (N=34)	No CSF leak (N=116)	
Non-Functioning	90 (60%)	9 (26.4%)	81 (69.8%)	<0.001
Functioning				
GH	28 (18.6%)	12 (35.3%)	16 (13.7%)	
PRL	20 (13.4%)	9 (26.4%)	11 (9.5%)	
ACTH	12 (8%)	8 (23.5%)	4 (3.4%)	

Out of the overall CSF leak; 26 cases (17.3%) had intraoperative leaks. Out of them; 5 patients (19.2%) had postoperative leaks after having repair of an intraoperative leak. 8 patients (23.5%) had a postoperative leak without an observed intraoperative leak, 2 of them had delayed leaks more than 30 days after surgery.

Out of 34 cases experienced overall CSF leak; the type of the adenomas was growth hormone-secreting pituitary adenomas ($n=12$, 35.2%), prolactin-secreting pituitary adenomas ($n=9$, 26.4%), non-functioning pituitary adenomas ($n=9$, 26.4%), and adrenocorticotrophic hormone-secreting adenomas ($n=8$, 21.1%). Radiological analysis of tumors in patients developed CSF leaks revealed: suprasellar extension was reported in 17 pituitary adenomas (50%), cavernous sinus invasion in 13 patients (38.2%), and hydrocephalus in 4 patients (11.6%). The mean largest tumor size was 3.1 ± 1.14 cm³ (Table 1).

Among the 34 cases with overall CSF leakage; 8 cases (23.5%) were recurrent adenomas. 6 cases of them (17.6%) had previous trans-sphenoid surgery only while the other 2 (5.8%) offered 3-dimensional radiotherapy after the initial trans-sphenoidal surgery. 4 cases (11.7%) developed CSF leakage while the surgery was done urgently for pituitary apoplexy.

Univariate analysis of different factors affecting overall leaks revealed: Patients in CSF leak group had mean BMI values 35.5 ± 2.53 kg/m² and patients had not experienced CSF leak had mean BMI values 29.56 ± 1.58 kg/m², ($P<.001$). CSF leak rate was 35.3% in patients with a BMI >35 kg/m², compared with 17.6% in patients with a BMI <25 kg/m² ($P=.007$). Higher rates of CSF leak were found in patients who had suprasellar extension (50%) compared to (19.8%) in non leak group ($P<.001$), hydrocephalus (11.6%) in leak group vs (1.6%) in non-leak group ($P<.001$), recurrent tumors (23.5%) in leak group vs 6.8% in non-leak group ($P<.001$). Urgent surgical intervention for apoplexy needed for 13 patients; 4 patients experienced CSF leak (11.6%) of total leak, and 9 patients without leak (7.7%) of total non-leak), ($P=.054$) (table 1).

Patients in the leak group had mean tumor size 3.1 ± 1.14 cm³ while patients without leaks had mean maximal tumor diameters 2.7 ± 0.91 cm³ ($P=.002$). The incidence of diabetes insipidus was significantly higher in the leak group (11.7%) compared to the non leak group (1.7%) ($p=.030$). Multiple logistic regression model analysis (Table 2) revealed that BMI, recurrent cases, hydrocephalus, and suprasellar extension, were statistically significance in relation to incidence of overall CSF leak.

Table 2. Multiple logistic regression model analysis of factors affecting incidence of CSF leaks.

CSF leak	95%CI	Odds Ratio	P value
Overall:			
BMI	1.03-1.09	1.05	0.017
Suprasellar	1.36-3.41	2.10	0.006
Hydrocephalus	1.41-5.23	2.53	0.007
Recurrence	1.02-2.21	3.21	0.041
Intraoperative:			
BMI	1.03-1.09	1.05	0.011
Suprasellar	1.49-3.98	2.48	<0.001
Hydrocephalus	1.56-5.78	3.10	0.003
Postoperative:			
BMI	1.02-1.11	1.03	0.033
Hydrocephalus	1.13-9.8	3.89	0.010

Univariate analysis of different factors affecting intraoperative leaks revealed (table 3): No statistical significance found between leak and non-leak groups as regard previous skull base radiation, pituitary apoplexy, and cavernous sinus invasion. Patients who had mean BMI values 33.5 ± 2.43 had a significant incidence of CSF leak compared to patients had 30.12 ± 2.11 kg/m², ($P<.001$). Higher rates of intraoperative CSF leak were found in patients who had suprasellar extension, hydrocephalus, and recurrent tumors. Multiple logistic regression model analysis (Table 2) revealed that BMI, hydrocephalus, and suprasellar extension, were significantly correlated with incidence of intraoperative CSF leaks.

Table 3. Perioperative univariate variable analysis of factors affecting incidence of intraoperative CSF leak.

Variable	Mean±SD or (n,%)		P value
	Intraoperative CSF leak (n=26)	No CSF leak (n=124)	
Age (years)	44.15±7.34	43.95±6.23	.642
Gender (male)	15,57.6%	52,41.2%	.261
BMI (kg/m ²)	33.5±2.43	30.12±2.11	<.001
Hypertension	13,50%	32,25.8%	.053
Empty sellae	0	2,1.6%	.065
Preoperative radiation	1,3.8%	3,2.4%	.421
Recurrence	7,26.9%	9,7.2%	<.001
Pituitary apoplexy	3,11.5%	10,8.1%	.063
Hydrocephalus	3,11.5%	3,2.4%	<.001
Max tumor size	2.9±1.1	2.02±.83	.002
Suprasellar	16,61.5%	24,19.3%	<.001
Cavernous sinus	17,65.3%	29,23.3%	.002
Non-Functioning	15,57.7%	75,60.5%	.501
Functioning			
GH	8,30.7%	20,16.1%	
PRL	7,26.9%	13,10.4%	.002
ACTH	5,19.2%	7,5.6%	

Univariate analysis of different factors affecting postoperative CSF leak revealed (Table 4). No statistical significance found between leak and non-leak groups as regard previous skull base radiation, pituitary apoplexy, and cavernous sinus invasion.

Mean BMI values for patients with CSF leak was 34.5 ± 5.3 while mean BMI values for patients in non-leak group was 30.12 ± 3.62 ($P = .003$). Postoperative CSF leak was observed in older patients (mean age, 49.6 ± 14.3 vs 41.5 ± 11.7 years; $P = .038$). Multiple logistic regression model analysis (Table 2) revealed that, BMI and hydrocephalus were significantly correlated with occurrence of postoperative CSF leaks.

Table 4. Perioperative univariate variable analysis of factors affecting incidence of postoperative CSF leak.

Variable	Mean±SD or (n,%)		P value
	Postoperative CSF leak (n=13)	No CSF leak (n=137)	
Age (years).	49.6±14.3	41.5±11.7	.038
Gender (male)	7,53.8%	60,43.7%	.687
BMI (kg/m ²)	34.5±5.3	30.12±3.62	.003
Hypertension	8,61.5%	47,34.3%	.052
Empty sellae	1,7.6%	1,0.7%	<.001
Preoperative radiation	1,7.6%	3,2.1%	.420
Recurrence	9,69.2%	7,5.1%	<.001
Pituitary apoplexy	2,15.2%	11,8%	1.0
Hydrocephalus	4,30.4%	2,1.4%	<.001
Maximum tumor size	3.5±1.3	2.9±1.1	.019
Suprasellar	8,61.5%	32,23.3%	<.016
Cavernous sinus	2,15.2%	44,32.1%	.002
Non-Functioning	6,45.6%	84,61.3%	.564
Functioning			
GH	3,23.1%	25,18.2%	
PRL	2,15.2%	18,13.1%	.012
ACTH	2,15.2%	10,7.2%	

Higher postoperative leak rate occurred in patients underwent septal flap repairs in comparison to other repair techniques (54% vs 30.7, 15.3%, $P = .063$) (table 5). Only 3 patients with intraoperative leak and 8 patients with postoperative leak were managed by using lumbar drains.

Table 5. Methods of sellar reconstruction for intraoperative CSF leaks and the rates of resulted postoperative leak.

Reconstruction technique	Postoperative CSF leak= 13 (n,%)
Septal flap	7,54%
Middle turbinate flap	4,30.7%
Multilayer reconstruction	2,15.3%

4. Discussion

CSF leak is one of the most common complications associating trans-sphenoid approach for removing pituitary adenomas [3]. Despite its well-known and evident prevalence, there are limited research studies investigating the risk factors associated with increased rate of CSF rhinorrhea and its clinical consequences [16].

Endoscopic skull base surgeons treating patients with pituitary adenomas can potentially change or modify their clinical management strategy to minimize the incidence of CSF leakage and its subsequent morbidities [17]. Prediction

of the possibility for intraoperative or postoperative CSF leakage in endoscopic endonasal surgery for pituitary adenomas is of great interest and is discussed in some the recent publications [5, 18].

Identification of such risk factors enables the surgeon to plan initially to avoid intra-operative CSF leakage and to prepare for how to deal with such complication if occurred [13]. Our current study reported an overall incidence of CSF leakage in 22.6% of cases operated upon for pituitary tumors using the endoscopic trans-sphenoid approach.

The incidence of postoperative CSF leakage in association with endoscopic trans-sphenoid approach for pituitary adenomas ranged between 1.4 and 16.9% in many series [1, 17], our rate of postoperative CSF leak was 8.6%. Although statistically insignificant; we had a slight female predominance in the incidence of CSF leakage which is same in some other studies that reported high incidence of CSF leakage in females [17].

There is a significant association between elevated BMI and both intraoperative and postoperative CSF leakage [17, 19]. Theories suggest that increase in pleural pressure and cardiac filling pressure may impede the brain venous return which cause increase in the intracranial venous pressure and hence increase the ICP. This pathophysiology is widely accepted in the pathogenesis of benign intracranial hypertension and empty sellae syndrome [20].

Ivan *et al.* found that increased BMI was associated with a higher incidence of postoperative CSF leakage in a cohort of 98 consecutive patients with expanded endoscopic trans-sphenoid approach performed at the University of California [13]. In current study of 150 patients, overall CSF leak was in 34 cases (22.6%); there was a statistically significant association between elevated BMI and both intraoperative and postoperative CSF leak ($p < 0.001$).

Although relatively uncommon, intraventricular extension had the greatest association with a postoperative CSF leak in many studies [13, 17]. This association is likely due to the increased risk of a high flow leak. However, in this study, 6 cases with intraventricular extension have been encountered. In addition, suprasellar extension had an interesting impact on the CSF leak especially the intraoperative in many studies [12, 21]. In our study we encountered statistically significant association between suprasellar tumor extension and the risk of CSF leak ($p < .001$).

This study copes with the literature in the identified risk factors like the high BMI, the presence of suprasellar tumor extension, the operated recurrent cases, the irradiated cases, the presence of intraoperative CSF leak [1, 13, 19, 20].

Regarding prior treatment; Nishioka *et al.* found that previous trans-sphenoidal surgery and skull base radiation were each in dependent risk factor for occurrence of postoperative CSF rhinorrhea [12]. Among our total 150 cases; there were 16 cases of recurrent adenomas (10.6%). Out of recurrent cases; 8 patients developed CSF leak (50%). While, 134 denovo cases only 26 cases (18.1%) developed CSF leak. In our study; we found statistical significance between recurrence and previous radiotherapy with the risk

of postoperative CSF leakage ($p < .001$).

The routine usage of lumbar drain with endoscopic trans-sphenoid approach is a matter of great debate and there is still some debate about its value with occurrence of intra-operative and post-operative CSF leakage [14, 22]. Many studies had underestimated its benefit in management of CSF rhinorrhea associating endoscopic trans-sphenoid surgery for pituitary adenomas [23]. Other studies considered the pattern of CSF leakage and recommended not to use lumbar drains for low-flow leakage and insert lumbar drain for high flow leakage with known or suspected intracranial hypertension or high possibilities for reconstruction failure [23]. In this study the authors limited the use of lumbar drain for cases of high flow CSF leak. However, in cases of low flow CSF leak lumbar drain was not performed. Lumbar drain was inserted in 8 patients of the postoperative CSF leak group and in 3 patients of the intraoperative CSF non-leak group.

Many reconstruction methods for the sella were advocated over the past few years [9, 11]. Many studies depend on fat or fascia lata for reconstruction while others use the previously described Hadad nasoseptal flap [10, 14, 22]. Intraoperative management of CSF leak depend on immediate surgical decision-making, which depend on factors such as surgery extensiveness, surgeon experience, specialty training (neurosurgery vs. otolaryngology) [3]. In this study the authors had the opinion that, when low-flow CSF leak was inspected, an autologous fat or fascial at a graft was placed with in the dural defect as an inlay graft, bone chips from the posterior septum were used as onlay graft. The authors covered all this with posterior septal flap. On the situation that high-flow CSF leak occurred, combined use of fat and fascia lata and or a vascularized pedicled nasoseptal flap was harvested from nasal septum and covered on the overlay graft.

Some studies had investigated the type of adenoma as an impact factor for postoperative CSF leak [17, 18]. However, the type of adenoma has not affected the rate of CSF leak in a statistically significant [17]. In this study, we noticed a higher incidence of postoperative CSF leak in cases of acromegaly and Cushing type of adenoma; one case associated with empty sella syndrome. This difference from the literature can be explained by the great anatomical variation of the skull base in these two types of adenomas [4, 21].

5. Conclusion

Prediction of CSF leak and good identification of risk factors are of great importance in endoscopic transsphenoidal surgery for pituitary adenoma. Elevated BMI, suprasellar extension of the tumor, recurrence or previous radiation and special types of adenoma are all important risk factors that have been proved in this study to have statistically significant association with the incidence of CSF leak. In high risk patients for CSF leakage; the surgical team should prepare a good and precise reconstruction plan to deal with occurrence of CSF leak.

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