Risk Factors Impacting Intra- and Postoperative Cerebrospinal Fluid Rhinorrhea on the Endoscopic Treatment of Pituitary Adenomas: Retrospective Experience From 250 Patients

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Research

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Abstract

Aim: We aimed to identify the risk factors associated with intra- and postoperative cerebrospinal fluid leakage in pituitary adenomas treated by endoscopic transsphenoidal surgery.

Material and methods: A retrospective analysis of 250 pituitary adenoma cases from January 2017 to December 2019 at our hospital was conducted; all patients underwent endoscopic endonasal transsphenoidal surgeries. A univariate analysis and multivariate analysis was performed to investigate the risk factors associated with intra- and postoperative CSF rhinorrhea.

Results: Eighty(32.0%) and nine(3.6%) patients had intraoperative and postoperative CSF leakages, respectively. Tumor size was an independent risk factor for intraoperative CSF leakage (OR, 1.229; 95% CI, 1.133–1.334; $P<0.001$); intraoperative CSF leakage was an independent risk factor for postoperative CSF leakage (OR, 7.707; 95% CI, 1.336–44.455; $P=0.022$). Chronic respiratory disease (OR, 57.500; 95% CI, 8.031–411.682; $P<0.001$) was also an independent risk factor for postoperative CSF leakage; vascularized septal mucosal flap was a protective factor for such (OR, 0.107; 95% CI, 0.013–0.894; $P=0.039$).

Conclusion: Intraoperative CSF leakages are more likely to occur in large pituitary adenomas; in the presence of intraoperative CSF leakages, postoperative CSF rhinorrhea is very likely to occur. Patients with chronic respiratory disease are also more likely to develop postoperative CSF leakages. However, the sellar base reconstructed using vascularized nasal septal flaps can significantly decrease the risk for such. Knosp grade, degree of tumor resection, postoperative lumbar subarachnoid drain use did not seem to have effect on the postoperative CSF rhinorrhea.

Introduction

Pituitary adenomas account for 15% of all intracranial tumors.¹ Endoscopic endonasal transsphenoidal surgery (EETS) has become the standard surgical treatment for pituitary adenomas, it is a reasonably safe procedure with low morbidity, particularly in experienced hands.^{2–4} However, postoperative cerebrospinal fluid (CSF) leakage is a major life-threatening complication following EETS,³ which may lead to meningitis⁵ or tension pneumocephalus,⁶ and is associated with a prolonged hospitalization, thus, is a potentially life-threatening complication. The incidence of such complications ranges from 0.5 to 15% following EETS³. To decrease the rates of such complications, elucidating the risk factors that affect the incidence of intra- and postoperative CSF leakage will be helpful. However, risk factors that predispose to both an intraoperative and postoperative leak remain poorly defined. In the present study, we retrospectively reviewed 375 serial cases of pituitary adenomas that treated by EETS by one surgeon. Our primary aim was to identify the predictors of intra- and postoperative CSF leakages in patients who underwent endoscopic resection of pituitary adenomas to inform patients better and educate surgeons on this potential risk.

Material And Methods

Patient population and data collection

A retrospective review of 315 consecutive patients with pituitary adenoma from January 2017 to December 2019 was conducted. All patients were followed up for 1 to 3 years with an average follow-up period of 15.6 months. All patients underwent initial EETS by a single surgeon(Y.J.). The study was approved by the ethics committee of our hospital. Inclusion criteria were as follows: 1) a histological diagnosis of pituitary adenoma, 2) primary tumor, 3) tumor was resected by EETS completely, 4) The operation was entirely performed by one surgeon(Y.J.), 5) Records of medical data are complete. Patients without complete documentation of the these data, and patients with tumor recurrence, prior skull-base operation, and history of radiation therapy or chemotherapy were all excluded in this study.

The following data were collected retrospectively from the medical records: Demographic data, including age, race, gender and body mass index (BMI). Comorbidity, patient history, and perioperative data, including hypertension, diabetes mellitus, coronary heart disease, chronic pulmonary disease, preoperative administration of bromocriptine. Tumor characteristics, including tumor size, consistency of the adenoma, adenoma pathology type, the Grade of knosp, hemorrhage into adenoma, the extent of excision of the tumor. Other recorded features were reconstructive techniques, and the use of CSF diversion. The primary outcome was intra- and postoperative CSF leak.

Surgical procedure and skull base reconstruction

All patients underwent EETS for the resection of their tumors. After infiltrating the local nasal mucosa with adrenalin and lidocaine, we performed middle turbinate reductions bilaterally, and a VNSF was then created for those large adenomas(≥ 10 mm). Diamond burs were used to burr down the posterior septum, and a sphenoidotomy was enlarged using a microdebrider; the back wall of the sphenoid and the borders of the sella were visualized. The base of the sella range was located by neuronavigator, and then opened using a high-speed drill and enlarged using rongeurs. A cruciate dural incision was created; thereafter, the tumors were resected using suction and ring curettes within the pseudo capsule of the pituitary adenoma. To detect occult intraoperative CSF leakage before closure, we occasionally use the Valsalva manoeuvre.

In the absence of CSF leakage during EETS, we perform either no packing or packing only with absorbable hemostatic gauze (Surgicel) within the sella, and covered by one layer of synthetic dura, finally laid over the surface with fibrin glue or VNSF(for large adenomas). If there is evidence of minor intraoperative CSF leakage, we utilize a fat graft packing of the sella, and perform careful reconstruction of the floor of the sella with one layer of synthetic dura + VNSF or a free graft harvested from the nasal mucosa (for microadenomas), the surface of above three repair materials usually fixed with fibrin glue. In cases with major CSF leakage, same as minor CSF leakage repair with the addition of a lumbar CSF diversion was used immediately for 5–7 days. The sella was supported by a foley balloon catheter (12–14 French) for 5–7 days.

Diagnosis and management of cerebrospinal fluid leakage

The diagnosis of a CSF leak was made as follows: (I) intra-operative CSF leak diagnosis, (1) intrasellar and (or) parasellar outflow of clear fluid, and (2) valsalva maneuver was performed when necessary; (II) post-operative CSF leak diagnosis, (1) clinical nasal outflow and positive glucose outflow, and (2) nasal endoscopic examination was performed when necessary. Postoperatively, patients with minor and intermittent CSF leakage were treated with bed rest (a posture that head is raised 30 degrees), prophylactic antibiotics, and limited activity, while, patients with major and persistent CSF leakage were treated with CSF diversion in a way of lumbar drains. A lumbar drains system would also performed for patients who failed in bed rest treatment for 7 days. All patients that failed in CSF diversion treatment (≥ 7 d) required reoperation via EETS.

Statistical methods

Categorical variables are presented as numbers and percentages and groups were compared using the Chi-Square and the Fisher's Exact test. Continuous variables are presented as mean and standard deviation and compared using the two-sided unpaired t-test. Factors predictive for CSF leakage in the univariate analysis ($p < 0.05$) were entered into a step-wise binary logistic regression model to identify independent factors for intra- and postoperative CSF leakage. Statistical analysis was performed using SPSS version 22.0 (IBM Corporation, Armonk, NY). A p -value < 0.05 was considered as statistically significant.

Results

Patient characteristics

Among 315 consecutive patients diagnosed with pituitary adenomas, a total of 250 patients met the inclusion criteria and included in this study from January 2017 to December 2019 at our institution. The average age of the patients was 44.1 ± 12.3 years. The mean hospitalization time was 8.4 days. The pathology included 187 (74.8%) nonfunctioning adenomas, 40 (16.0%) GH-secreting pituitary adenomas, 3 (1.2%) PRL-secreting pituitary adenomas, 20 (8.0%) ACTH-secreting pituitary adenomas. There were 30 (12.0%) case of microadenomas, 205 (82.0%) cases of macroadenomas and 15 (6.0%) cases of giant adenomas.

Intra- and postoperative CSF leakages

Intraoperative CSF leaks were observed during surgery in 80 patients (32.0%), and postoperative CSF leaks occurred in 9 patients (3.6%), respectively. Of the 80 cases with intra-operative leaks, the number of minor and major CSF leaks was 61, and 19, respectively. Postoperative CSF leaks occurred in 9 patients (3.6%), including 7 patients with intraoperative CSF leaks and 2 patients without a recognized intraoperative CSF leak. Among 9 cases with postoperative CSF rhinorrhea, 6 cases were initially treated with 5–7 days of passive lumbar drainage, including bed rest, prophylactic antibiotics, and limited activity, whereas another 3 patients required surgical repair through a trans-sphenoidal approach. All those nine patients had resolution of their CSF leaks finally, no failures. Four patient with postoperative

CSF leak was complicated with meningitis 2–7 days after EETS. Those patient underwent meropenem + vancomycin treatment for 14 days and was discharged from hospital without problems.

Univariate analysis

In the univariate analysis, there were three factors associated with an increased intraoperative CSF leakage rate (Table 1): (1) BMI ($P = 0.013$), (2) tumor size ($P < 0.001$), (3) consistency of the adenoma ($P = 0.032$). Similarly, predictors of postoperative CSF leaks on univariate analysis were: (1) chronic respiratory disease (CRD) ($P < 0.001$), (2) degree of tumor resection ($P = 0.011$), and (3) intraoperative CSF leakage ($P = 0.021$); only one factor was associated with a decreased postoperative CSF leakage rate: sella reconstructed by abdominal fascial graft + synthetic dura + VNSF ($P < 0.001$).

Table 1. Univariate analysis of impact of clinical characteristics associated with intraoperative CSF leak

Variable	No intraop leak(n=170)	Intraop leak(n=80)	P value
Gender			
Female	82(48.2%)	48(60.0%)	0.219
Male	88(51.8%)	32(40.0%)	
Age(̄years)	44.15±14.52	44.13±15.85	0.992
BMI(kg/m²)			
≤18.5	24(14.1%)	20(25.0%)	0.013
18.5-23.9	88(51.8%)	50(62.5%)	
24-27.9	44(25.9%)	6(7.5%)	
≥28.0	14(8.2%)	4(5.0%)	
Hypertension			
No	144(84.7%)	60(75.0%)	0.191
Yes	26(15.3%)	20(25.0%)	
Diabetes			
No	154(90.6%)	72(90.0%)	1.000
Yes	16(9.4%)	8(10.0%)	
CRD			
No	162(95.3%)	72(95.0%)	1.000
Yes	8(4.7%)	4(5.0%)	
Coronary heart disease			
No	154(90.6%)	76(95.0%)	0.621
Yes	16(9.4%)	4(5.0%)	
Knosp Grade			
0	28(16.5%)	16(20.0%)	0.641
1-2	106(62.4%)	40(50.0%)	
3-4	36(21.2%)	24(30.0%)	
Tumor size	16.84±6.16	26.20±7.83	<0.001

Consistency of the adenoma			0.032
Tenacious	50(29.4%)	57(71.3%)	
Soft	120(70.6%)	23(28.7%)	
Degree of tumor resection			0.248
GTR	152(89%)	66(83%)	
STR	14(8.2%)	12(15%)	
PR	4(2.8%)	2(2%)	
Pathology			0.972
NF	124(72.9%)	63(78.8%)	
ACTH	16(9.4%)	4(5.0%)	
GH	28(16.5%)	12(15%)	
PRL	2(1.2%)	1(1.2%)	

BMI: body mass index CRD: chronic pulmonary disease CSF: cerebrospinal fluid

Multivariate analysis

The multivariate analysis was performed using variables significantly correlated with intraoperative CSF leakage. However, in the multivariate analysis (Table 2), only the tumor size ($P < 0.001$; OR, 1.229) was independently associated with an increased intraoperative CSF leakage rate. Similarly, the multivariate analysis was performed using variables significantly correlated with postoperative CSF leakage (Table 4) and indicated that CRD ($P < 0.001$; OR, 57.500) and intraoperative CSF leakage ($P = 0.022$; OR, 7.707) were the independent risk factors for postoperative CSF leakage; further, the use of VNSF + abdominal fat ($P = 0.039$; OR, 0.107) was an independent protective factor for postoperative CSF leakage.

Table 2. Multivariate analysis of impact of clinical characteristics upon intraoperative CSF leak

Variable	OR	95%CI for OR	P value
Tumor size	1.229	1.133-1.334	<0.001

Table 3. Univariate analysis of impact of clinical characteristics associated with postoperative CSF leak

Variable	No postop leak(n=241)	postop leak(n=9)	P value
Gender			
Female	129(53.5%)	5(55.6%)	1.000
Male	112(46.5%)	4(44.4%)	
Age(years)	44.07±14.67	45.25±18.99	0.829
BMI(kg/m ²)			
≤18.5	40(16.6%)	2(22.2%)	0.462
18.5-23.9	141(58.5%)	2(22.2%)	
24-27.9	44(18.3%)	4(44.5%)	
≥28.0	16(6.6%)	1(11.1%)	
Hypertension			
No	192(79.7%)	6(66.7%)	0.979
Yes	49(20.3%)	3(33.3%)	
Diabetes			
No	212(88.0%)	7(77.8%)	0.565
Yes	29(12.0%)	2(22.2%)	
CRD			
No	230(95.4%)	5(55.6%)	<0.001
Yes	11(4.6%)	4(44.4%)	
Coronary heart disease			
No	216(89.6%)	7(77.8%)	0.497
Yes	25(10.4%)	2(22.2%)	
Tumor size	19.56±7.82	23.75±10.35	0.154
Pathology			
NF	181(75.1%)	6(66.7%)	0.383
ACTH	19(7.9%)	1(11.1%)	
GH	38(15.8%)	2(22.2%)	
PRL	3(1.2%)	0(0.00%)	
Consistency of the adenoma			

Tenacious	119(49.4%)	5(55.6%)	0.451
Soft	122(50.6%)	4(44.4%)	
Knosp Grade			0.864
0	42	1	
1-2	145	5	
3-4	54	3	
Degree of tumor resection			0.011
GTR	208	6	
STR	27	3	
PTR	6	0	
Intraoperative CSF leak			0.021
No	173(71.8%)	2(22.2%)	
Yes	68(28.2%)	7(77.8%)	
Sella reconstruction methods			<0.001
synthetic dura+biological glue	166(68.9%)	3(33.3%)	
abdominal fat+ dura+free graft	28 (11.6%)	6(66.7%)	
abdominal fat+ dura+VNSF	47 (19.5%)	0(0%)	
lumbar subarachnoid drain			0.286
No	226(93.8%)	7(77.8%)	
Yes	15(6.2%)	2(22.2%)	

BMI: body mass index CRD: chronic pulmonary disease VNSF:vascularized nasal septal flap CSF: cerebrospinal fluid NF: no functioning GTR: gross total resection STR: sub-total resection PR: partial resection

Table 4. Multivariate analysis of impact of clinical characteristics upon postoperative CSF leak

Variable	OR	95%CI for OR	P value
CRD	57.500	8.031-411.682	<0.001
Intraoperative CSF leak	7.707	1.336-44.455	0.022
VNSF+ abdominal fat graft	0.107	0.013-0.894	0.039

CRD=chronic pulmonary disease VNSF=vascularized nasal septal flap

Discussion

EETS continues to improve owing to recent advances in equipment, hemostatic reagents, and closure techniques; the incidence of CSF leakage has been reduced to a range from 0.5 to 12% following EETS.^{1,7-9} However, there are still some factors unrelated to surgical skills that could impact the rates of intra- and postoperative CSF leakage; those factors have been poorly defined, and our data suggest that certain factors can predict a greater likelihood of CSF leakages both in the intra- and postoperative periods of EETS.

In studies of CSF leakage in pituitary adenomas after transnasal surgery, most of the researchers found that CSF leakage occurred in most patients with an intraoperative CSF leakage;^{3,4,10} thus, intraoperative CSF leakage seems to be an important risk factor for postoperative CSF leakage. Similarly, this conclusion was also confirmed in our study. Nine patients had a postoperative CSF leakage, and seven of them had an intraoperative CSF leakage; the final multivariate regression analysis showed intraoperative CSF leakage as an independent risk factor for postoperative CSF leakage (OR, 7.707; P = 0.022).

Based on the results above, we can see that it is important to prevent intraoperative CSF leakage to reduce the rate of postoperative CSF leakage; understanding the risk factors of intraoperative CSF leakage is beneficial in its management and prevention of postoperative CSF leakage. It is obvious that all the factors that can induce diaphragma sellae rupture can lead to a CSF leakage; thus, the factors impacting the rupture of the diaphragm sellae can also lead to intraoperative CSF leakages. In our reports, we observed the significant difference in the tumor size between those who had an intraoperative CSF rhinorrhea and those who did not (16.84 ± 6.16 vs 26.20 ± 7.83 ; $P < 0.001$). Zhou et al.⁴ also reported a high incidence of intraoperative CSF leakage following a large size pituitary adenoma resection; the final multi-factor regression analysis demonstrated that it was an independent risk factor for intraoperative CSF rhinorrhea. The mechanism of the tumor size being a risk factor of CSF leakage in surgery may be due to suprasellar extension in large size tumor, which can lead to a rather thin diaphragm sellae. Therefore, we think a gentle manipulation is necessary for large pituitary adenomas to avoid the rupture of a rather thin diaphragm sellae in surgery. At the same time, we can also remove the tumor in the following order: rear, two sides, and front to avoid dropping the diaphragma sellae too early and too fast, which may lead to its rupture and consequently CSF leakage.

Our results revealed that CRD had increased the risk of postoperative CSF leakage (OR, 57.5; $P < 0.01$). To our knowledge, this has never been reported in the literature until now. This result may be related to the increased intracranial pressure during the acute onset of CRD. The increased intrathoracic pressure leading to a decreased blood flow of the jugular vein resulting in an increased intracranial pressure may cause herniation of the repaired material from the sellar base and CSF leakage. Two other studies^{11,12} had proven the mechanism of an increased intracranial pressure playing an important role in the occurrence of postoperative CSF leakage or a spontaneous CSF leakage. Hanba et al.¹² discovered that patients with asthma are more likely to have CSF leakage than patients without asthma after transnasal surgery; further, the rate of postoperative CSF leakage in these two groups was 4.7% and 2.7%, respectively. Fleischman et al.¹¹ found that patients with obstructive sleep apnea are more likely to develop a spontaneous CSF leakage.

Previous studies^{3,13} have already reported that BMI was a risk factor for postoperative CSF leakage following EETS, however, incidence of CSF leakage did not correlate with BMI in our series. Dlouhy et al.¹³ and Karnezis et al.³ both indicated that BMI was a risk factor for postoperative CSF leakage. However, the average BMI of the CSF leakage group compared with that of the non-CSF leakage group in these two studies was 33.1:30.3 kg/m² and 39.2:32.9 kg/m², respectively; both of their patients' average BMI was greater than 30 kg/m². In our study, the average BMI was ~ 21.80:21.66 kg/m², which was lower than those in the previous studies. We think it is possible that the average BMI in our patients was not elevated enough to lead to a spontaneous increase in the intracranial pressure, which can result in postoperative CSF rhinorrhea.

Some studies have suggested that a VNFP can reduce the incidence of postoperative CSF leakage to less than 6%.^{14–16} Currently, using vascularized mucosal flaps has become a recognized method for sellar base reconstruction. Obviously, the incidence of postoperative CSF leakage in our patients significantly reduced by the use of VNFP and abdominal fascial graft. The blood supply of the VNFPs was mainly derived from the septal artery, which is rich in blood flow; thus, the survival rate was higher than those in any other non-vascular mucosal flaps.¹⁴ El-sayed et al.¹⁴ also pointed out that the atrophy of the mucous with a VNFP was smaller than that with a non-vascular mucosa flap, which was not enough to detach the mucosal flap from the sellar base.

Whether the use of lumbar subarachnoid drains reduces the rates of postoperative CSF rhinorrhea remains controversial.^{17,18} Some researchers noted that the use of intraoperative lumbar subarachnoid drain did not significantly reduce the postoperative CSF leakage rate.^{19,18} However, Stokken et al.²⁰ indicated that in patients with a high-flow intraoperative CSF leakage, the use of a lumbar subarachnoid drain can immediately reduce the risk for postoperative CSF leakage. Conversely, our study found that the use of such did not significantly reduce the risk of postoperative CSF leakage. Using a lumbar subarachnoid drain can also easily lead to intracranial infection¹⁸ and prolonged hospitalization;¹⁹ thus, we think careful consideration in using a lumbar subarachnoid drain intraoperatively to prevent postoperative CSF leakage is necessary.

Conclusion

In the nasal transsphenoidal endoscopic resection of pituitary adenomas, patients with a large tumor should be strictly monitored for intraoperative CSF leakage; in the presence of intraoperative CSF leakage, sellar base defects should be more carefully repaired to avoid postoperative CSF leakage. The sella constructed by abdominal fat + VNFP can help lower the rate of postoperative CSF leakage; as such, a VNSF should be created ahead of time for these patients. For patients comorbidity with CRD, the postoperative management must be more cautiously provided, and respiratory management are necessary to reduce inflammatory reactions in the postoperative period. These measures can effectively reduce the risk of postoperative CSF leakage.

Declarations

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No

Conflicts of Interest

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Authors' contributions

YP conceived and designed the study. MW and YC performed the statistical analyses. YJ, MW, and YC contributed in collecting and interpreting data as well as in drafting and critically revising the manuscript. All authors approved the final version of the manuscript and are accountable for the accuracy and integrity in all aspects of the study.

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Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Second Xiangya Hospital of Central South University.

Consent for publication

This study was obtained informed consent from all patients.

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