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Prevalence of Cerebrospinal Fluid Rhinorrhea Following Trans-Sphenoidal Surgery for Pituitary Adenoma in Patients Referred to Loghman Hakim Hospital from 2016 to 2020

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Abstract

Background: Endoscopic endonasal transsphenoidal surgery is commonly used to remove pituitary adenomas. However, it can lead to cerebrospinal fluid (CSF) leakage, with an incidence of around 5% in sphenoid transnasal procedures and up to 20% in extended endonasal approaches. A retrospective study was conducted on 160 pituitary adenoma patients admitted to Loghman Hakim Hospital from 2016 to 2020 to evaluate the factors influencing CSF leak.

Aim: The aim of this study was evaluating the occurrence of cerebrospinal fluid leakage and analyzing the factors involved.

Methods: This is a retrospective analysis of patients diagnosed with pituitary adenoma at Loghman-Hakim hospital over four years. Demographic information, tumor characteristics, surgical procedures, and complications were collected. All patients gave their consent, and the study was approved by the ethics committee. Surgical procedures were conducted using a direct endonasal trans-sphenoidal approach under general anesthesia, and antibiotics were given. Statistical analysis was conducted using SPSS to evaluate the relation between measured variables and the occurrence of CSF leak.

Results: The study found that 19.4% of the patients developed CSF leak during their hospital stay. Age and body mass index (BMI) of patients with CSF leak significantly differed from those without. The size of the tumor did not differ significantly between patients with and without CSF leak. The only variable associated with CSF leak was sphenoid sinus anatomy.

Conclusion: The study concluded that older patients with a lower BMI and a larger defect size are more prone to CSF leak, but no significant difference was found in tumor size between the groups with and without CSF leak. Sphenoid sinus anatomy correlated with CSF leak, while other factors did not show any correlation with the incidence of CSF leak.

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Introduction

For the past two decades, the sphenoid transnasal endoscopic approach has been the primary surgical technique used to remove pituitary and other adenomas located in the

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sellar region (1, 2). Over the past few years, there have been significant advancements in surgical techniques and tools used in skull base surgery. One such method is endonasal surgery, which has made it possible to access midline lesions located beyond the sellar area, such as meningiomas in the front of the skull base, craniopharyngiomas, and large adenomas (3, 4).

Despite the numerous advantages of this less invasive method compared to transcranial approaches, there is one limited complication that needs to be addressed-cerebrospinal fluid leak and its associated complications such as meningitis, pneumocephaly, and low-pressure headache (5-9). Based on various studies, the incidence of cerebrospinal fluid leakage during surgery is most influenced by the techniques and methods used to repair skull base defects(4). Besides, factors such as the patient's history of previous surgery or radiotherapy, the size of the dura defect at the base of the skull, the patient's BMI, and the surgeon's experience are all mentioned as potential contributors to the amount of cerebrospinal fluid leakage after trans-endonasal sphenoid surgery (4, 5, 7, 10).

Studies show cerebrospinal fluid leakage occurs in 5% of patients in sphenoid transnasal procedures and up to 20% in extended endonasal methods (4, 7, 8). Trans-endonasal sphenoid surgery involves a variety of repair methods for the skull base. In most cases, the skull floor and dura defects are reconstructed using autograft fascia or synthetic materials, and glue tissue, which are strengthened with a merocele pack, nasal pack, or lumbar drain. The choice of dura repair method for the base of the skull depends on various factors, such as the size of the tumor, the extent of the dura defect, and the patient's condition. The surgeon's experience and the type of surgery being performed also play a role in the decision-making process (7, 11, 12).

As there is currently limited comparative evidence on the factors influencing the incidence of cerebrospinal fluid leakage, we conducted a study to evaluate this incidence in patients who were admitted to Loghman-Hakim Hospital from 2016 to 2020.

Methods

Study Population

Patients diagnosed with pituitary adenoma who were admitted to Loghman-Hakim hospital during four years were analyzed retrospectively. Patients who consented and suffered from pituitary adenoma were included, and the diagnosis was confirmed pathologically. Patients who had incomplete medical records were excluded. All patients were informed of the study's purpose and gave their consent. The study was approved by the ethics committee at Shahid Beheshti University of Medical Sciences and followed the declaration of Helsinki.

Data Collection

The study evaluated patients' demographic information, tumor size and type, defect size, cerebrospinal fluid leak, surgical and repair methods, the technique of repair, anatomical position, tumor invasion, and surgery complications. Radiological evaluations were performed, and the KNOSP criteria were calculated based on the results. The KNOSP criteria were established in 1993 and classify cavernous sinus invasion of pituitary tumor based on the relation of the pituitary tumor with the line between supraclonoid internal carotid artery (ICA) and intra-cavernous ICA on coronal magnetic resonance imaging.

Knosp classification is used to determine the invasion level of pituitary adenoma (PA). Knosp 0 indicates that the PA is medial to the medial tangent. Knosp 1 suggests that the PA extends to the space between the medial tangent and the intercarotid line. Knosp 2 indicates that the PA extends to the space between the intercarotid line and the lateral tangent. Knosp 3 suggests that the PA extends lateral to the lateral tangent, and Knosp 4 indicates a complete encasement of the intracavernous ICA.

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Surgical Procedure

All patients underwent a surgical procedure through a direct endonasal trans-sphenoidal approach using an operating microscope. The goal of the surgery was to remove the affected tissues while minimizing neural and vascular structure damage and reducing symptoms as much as possible. Patients were positioned supine with their head slightly raised and tilted back.

The surgery was performed under general anesthesia, and perioperative, intravenous, broad-spectrum antibiotics were given to all patients until nasal packing materials were removed. The surgical site was fully disinfected after administering general anesthesia. The surgery was performed using an endoscope, with a 0° or 30° 4-mm endoscope typically being used.

Most cases used a uni-nostril approach to minimize damage to the nasal mucosa, while a bilateral nostril technique was used when the operating space was narrow.

The nasal mucosa was covered with an epinephrine cotton pad. After hospital discharge, oral broad-spectrum antibiotics were prescribed for a week.

Statistical Analysis

The statistical analysis was conducted using SPSS. Qualitative parameters were described by frequency and percentage, while quantitative variables were reported by mean and standard deviation. Independent T-test and Mann-Whitney U test were performed to compare patients with and without CSF leak. Fisher exact test and chi-square test were conducted to evaluate the relation of measured variables and the occurrence of CSF leak.

Results

General characteristics

One hundred and sixty patients with pituitary adenoma were included. Out of the 160 patients who were studied, 31 of them (19.4%) developed CSF leak during their hospital stay. Out of these 31 patients, 21 (67.7%) had mild CSF leak while the remaining 10 (32.3%) had severe CSF leak. Table 1 shows a comparison of the demographic information between the groups that experienced CSF leak and those that did not. The results showed that there was a significant difference in the mean age (46.55 vs. 38.59, p=0.003) and BMI (27.45 vs. 29.32, p=0.032) between the two groups.

Table 1. Demographic information

	CSF leak		P-value
	Yes (n=31)	No (n=129)	
Age	46.55±13.39	38.59± 13.15	0.003
BMI	27.45± 3.47	29.32± 6.80	0.032
Sex			
Male	20(24.1)	63(75.9)	0.117
Female	11(14.3)	66(85.7)	
Past surgery			
Yes	3(18.8)	31(81.3)	0.947
No	28(19.4)	116(80.6)	

M±SD, N (%)

As shown in Table 1, the age and the BMI differed significantly between patients with and without CSF leak. Patents with CSF leak were older and had lower BMI.

Tumor size and CSF leak

The results of conducted test to evaluate to difference of tumor size in patients with and without CSF leak are listed in Table 2

As illustrated in Table 2, the CSF leak did not differ significantly between patients with macro- or microadenoma.

Also, the size of the tumor did not differ between the patients with and without CSF leak. However, the size of defect statistically varied between two groups.

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Other clinical findings

We evaluated the relation of sinus involvement, complications, Knosp, repair techniques, surgery approaches, sphenoid sinus anatomy, and CSF leak. The details are shown in Table 3.

Table 2. Clinical measurement

Micro-macro	CSF leak		P-value
	Yes (n=31)	No (n=129)	
Micro adenoma	2(9.1)	20(90.9)	0.189
Macro adenoma	29(21.0)	109(79.0)	

M±SD, N (%), *Mann-Whitney test

Table 3. Clinical findings

	CSF leak		P-value
	Yes	No	
Caverns Sinus			
Left	5(20.8)	19(79.2)	0.870*
Right	6(15.0)	34(85.0)	
Both-side	3(23.1)	10(76.9)	
None	17(20.5)	66(79.5)	
Knosp			
Knosp1	2(22.2)	7(77.8)	0.895*
Knosp2	3(15.8)	16(84.2)	
Knosp3	4(13.8)	25(86.2)	
Knosp4	4(21.1)	15(78.9)	
Suprasellar extension			
Yes	26(19.4)	108(80.6)	0.984
No	5(19.2)	21(80.8)	
Third ventricle			
Yes	11(20.4)	43(79.6)	0.820
No	20(18.9)	86(81.1)	
Sphenoid Sinus			
Yes	15(24.2)	47(75.8)	0.220
No	16(16.3)	82(83.7)	
Sub frontal			
Yes	2(14.3)	12(85.7)	0.614
No	29(19.9)	117(80.1)	
Cystic			
Yes	8(15.4)	44(84.6)	0.376
No	23(21.3)	85(78.7)	
Apoplexy			
Yes	5(21.7)	18(78.3)	0.757
No	26(19.0)	111(81.0)	
Apoplexy type			
Acute	5(22.7)	17(77.3)	>0.99*
Chronic	0(0.0)	2(100.0)	
Hydrocephalus			
Yes	1(33.3)	2(66.7)	0.478*
No	30(19.1)	127(80.9)	
Surgery approach			
ETSS	30(19.4)	125(80.6)	>0.99*
Extended	1(20.0)	4(80.0)	

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Repair technique			
Fat	30(19.5)	124(80.5)	>0.99*
Fascia	1(16.7)	5(83.3)	
Sphenoid sinus anatomy			
Pre sellar	8(38.1)	13(61.9)	0.046*
Sellar	23(17.4)	109(82.6)	
Conchal	0(0.0)	7(100.0)	

*Fisher Exact test

Table 3 illustrates the relation of CSF leak and other clinical findings. As demonstrated, the only variable that associated with CSF leak was sphenoid sinus anatomy (p-value<0.05).

Discussion

Cerebrospinal fluid (CSF) leak is a common complication that may occur after transsphenoidal surgery (TSS). This complication is associated with various health risks such as meningitis, intracranial infection, and CSF hypotension syndrome. These complications can lead to additional healthcare costs and significant morbidity, often requiring prolonged hospitalization, reoperation, and external lumbar drainage (ELD)(13, 14).

The possible cause of a cerebrospinal fluid (CSF) leak is a rupture in the arachnoid or the top saddle diaphragm, which can occur due to tumor resection and results in the outflow of cerebrospinal fluid from the nasal cavity(15).

In this study, we enrolled a hundred and sixty patients with PA who willingly underwent TSS. Afterwards, we compared the demographic variables, tumor size, Knosp, third ventricle and sinuses involvements, apoplexy incidence and type, surgery and repair techniques between patients with and without CSF leak.

In this survey, 19.4 % of studied cases developed CSF leak. The finding of this study is more than the estimated incidence in two meta-analyses conducted by Slot et al. and Borg et al. in which only 3.4%, and 8.9% of adults underwent TSS developed CSF leak, respectively (16, 17).

Previous studies showed that there is no difference in CSF incidence considering age and gender (11, 18-27). However, Caitlin et al. showed that younger patients had higher risk for developing CSF leak (28). Accordingly, the current study showed that the age significantly differed between two groups.

Several studies have shown that a high BMI is an independent predictor of postoperative CSF leakage after transsphenoidal surgery (TSS) (25, 28). This association could be attributed to the increased intra-abdominal pressure that is often linked to higher BMI (29). Likewise, we showed that the difference in BMI between patients with and without CSF leak was significant. Several studies have demonstrated that patients with giant adenomas are more susceptible to postoperative cerebrospinal fluid (CSF) leaks compared to those with microadenomas (20, 26).

It can be inferred that the occurrence of CSF leaks is more likely in patients with larger tumors (measured by diameter or volume) than those with smaller ones (30, 31). Despite previous findings, no significant difference was found in the incidence of CSF leaks regarding macro and microadenoma. However, the defect size significantly differed between the two groups.

Moreover, the suprasellar extension and invasiveness of pituitary adenoma may contribute to the development of CSF leakage, according to current knowledge(20). We found three studies that discussed the relationship between the suprasellar extension of pituitary adenoma and perioperative CSF leakage (32-34). While two studies used Wilson grades to determine the extent of suprasellar extension, one study simply described the tumor with or without suprasellar extension (33, 34). From one study, it was revealed that tumors with

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suprasellar extension had higher rate of leakage. However, this study did not find such relation. A meta-analysis conducted on suprasellar extension effect on CSF leak, but due to small studies and heterogenesity, the results were not trustworthy (35). Thus, the effect of suprasellar extension on CSF leak is not yet clear. We found no relation between supresellar extension and CSF leak. Although surgical techniques have significantly improved, cavernous sinus invasion still remains a significant factor in cerebrospinal fluid (CSF) leak due to the need for extensive surgery. This suggests that tumors infiltrating the cavernous sinus are more likely to cross the diaphragm, so increasing the risk of postoperative CSF leak (36).In a meta-analysis conducted by Slot et al. it was revealed that post-operative CSF leak is affected by cavernous sinus invasion(16). However, the finding of the current study is in contrast with the result of this meta-analysis. We found that sinus cavernous invasion does not significantly relate to CSF leak incidence. This opposition may be due to the fact that we have splited the cavernous sinus invasion based on the laterality. Furthermore, smaller sample size may be the reason.

Moreover, the infiltration was evaluated via Knosp. Jang et al. reviewed 331 patients who underwent endoscopic endonasal transsphenoid surgery (EETSS). Invasive adenoma in Knosp classification were associated with occurrence of complications after EETS (37). In this survey, the Knosp score did not associated with CSF leak. A critical period for extra-caution is the postoperative phase following resection of giant pituitary macroadenomas, particularly in cases of subtotal resection where the residual tumor is susceptible to apoplexy(38). In this study, we observed no difference between the two groups in terms of incidence of apoplexy and hydrocephalus.

The technique of surgery influences the post-opertive CSF leak. A meta-analysis conducted by Li et al. included 23 studies, and evaluated 2272 patients with pituitary adenoma. This meta-analysis compared two surgical techniques: endoscopic TSS and microscopic TSS. The results showed that endoscopic TSS led to a higher rate of complete tumor removal compared to microscopic TSS. Besides, endoscopic TSS did not significantly affect the risk of cerebrospinal fluid leak as opposed to microscopic TSS. On the other hand, endoscopic TSS significantly decreased the risk of septal perforation and did not appear to be associated with the risk of meningitis, epistaxis, hematoma, hypopituitarism, hypothyroidism, hypocortisolism, total mortality, or recurrence(39). We evaluated the relation of CSF leak incidence and surgery technique. It was revelaed that the incidence of CSF leak does not associate with surgery technique (either extended or endoscopic TSS).

Reconstructing the skull base is challenging due to the restricted working space, varying risk and morbidity profiles of repair materials, and the forces of gravity and overlying dependent intracranial structures that must be overcome using long rigid instruments (12).The repair strategies for intraoperative CSF leaks have primarily utilized autologous fat or fascial grafts, synthetic dural grafts, and mesh devices with varying levels of success. Sciarretta and colleagues conducted a study on 665 patients who had undergone surgery to remove pituitary adenomas. In cases where intraoperative CSF leaks were identified, only fat and mucoperiosteum grafts were placed. The study found that 128 patients (19.2%) required intraoperative repair for CSF leak, while 11 patients (8%) required postoperative CSF leak repair(40). In a study conducted by Dehdashti et al., where mostly macroadenomas were treated, autologous fat and fascia grafts were used in 200 cases to prevent intraoperative CSF leaks. Postoperative leaks occurred in only 3.5% of cases (40). Similarly, Berker et al. reported a low incidence rate of 1.3% of postoperative CSF leaks with the use of autologous fat and fascia grafts(41). Messerer

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et al. reported outcomes of 82 cases, where a combination of autologous fat and fascia grafts along with a synthetic dural graft was used. The study cited a 12.1% incidence rate of postoperative CSF leaks, but the lesion sizes were not reported (42).

In a study, an apposition graft was placed in all cases of identified intraoperative leaks, and in 92 patients as a preventive measure. Intraoperative leak incidence was 37.4%, postoperative leak incidence was 2.6%. Out of 375 patients who received graft placement, only 13 developed a postoperative CSF leak, indicating 96.5% success rate on the first attempt. Graft failure occurred in 2.8% of patients (43). In this study, majority of patients underwent fat graft, the rest received fascia graft. After conducting Fisher exact test, it was revealed that there is no asocition between repair technique and CSF leak occurrence. 19.5% of patients who had repair with fat had CSF leak. Thus rate was nealy the same in patients who underwnet repair with fascia.

Our retrospective study has various limitations, including incomplete data, patient compliance, admission rates, and information objectivity. Besides, this study was conducted as a single-centered, with low sample sizes, and the follow-up duration was relatively short.

Conclusion

In conclusion, older patients with lower BMI and bigger defect size tend to have mre CSF leak incidence. While tumor size did not differ between groups with and without CSF leak. Other factors did not relate to the CSF leak incidence.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethics

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