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ORIGINAL ARTICLE - PITUITARIES

Predicting post-operative cerebrospinal fluid (CSF) leak following endoscopic transnasal pituitary and anterior skull base surgery: a multivariate analysis

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Abstract

Background Post-operative CSF leak is the major source of morbidity following endoscopic transsphenoidal surgery. The purpose of this study was to identify factors associated with post-operative CSF leak in patients undergoing this surgery and facilitate the prospective identification of patients at higher risk of this complication.

Methods A review of a prospectively maintained database containing details of 270 endoscopic transsphenoidal operations performed by the senior author over a 9-year period was performed. Univariate analysis was performed using the Chi-squared and Fisher's exact tests, as appropriate. A logistic regression model was constructed for multivariate analysis.

Results The rate of post-operative CSF leak in this series was 9%. On univariate analysis, previous surgery, resection of craniopharyngiomas, adenomas causing Cushing's disease and intra-operative CSF leaks were associated with an increased risk of post-operative CSF leak. The use of a vascularised nasoseptal flap and increasing surgical experience were associated with a decreased rate of CSF leak. On multivariate analysis, a resection of tumour for Cushing's disease (OR 5.79, 95% CI 1.53–21.95, $p = 0.01$) and an intra-operative CSF leak (OR 4.56, 95% CI 1.56–13.32, $p = 0.006$) were associated with an increased risk of post-operative CSF leak. Increasing surgical experience (OR 0.14, 95% CI 0.04–0.46, $p = 0.001$) was strongly associated with a decreased risk of post-operative CSF leak.

Conclusions Increasing surgical experience is a strong predictor of a decreased risk of developing post-operative CSF leak following endoscopic transsphenoidal surgery. Patients with Cushing's disease and those who develop an intra-operative CSF leak should be managed with meticulous skull base repair and close observation for signs of CSF leak post-operatively.

Keywords CSF leak · Endonasal endoscopic surgery · Transsphenoidal surgery, skull base surgery

This article is part of the Topical Collection on *Pituitaries*

Presentation
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Introduction

The use of the endoscopic endonasal approach to pituitary tumours has expanded hugely since it was first proposed by Carrau et al., and this approach has largely replaced traditional microscopic approaches in many centres [1, 4]. More recently, endoscopic approaches to tumours located outside of the sella have been proposed: referred to as 'expanded' endonasal approaches. This approach uses an endonasal approach to access the anterior, middle and posterior cranial fossae, and its use has been advocated in the management of meningiomas, craniopharyngiomas, as well as posterior fossa meningiomas and chordomas [19, 22, 25].

A common complication associated with these approaches is post-operative cerebrospinal fluid (CSF) leak. Patients who develop a post-operative CSF leak are at increased risk of developing post-operative meningitis and often require re-operation to identify and repair the CSF fistula [23, 28]. Moreover, the length of stay and healthcare-associated costs for patients who suffer this complication are significantly increased [13]. Prospective identification of patients at increased risk of this complication would better inform the management of such patients. The aim of this study was to identify factors predictive of post-operative CSF leak in patients undergoing endoscopic transsphenoidal surgery (ETSS) and expanded endoscopic transsphenoidal surgery (EETSS).

Methods

The results from this study were obtained following a review of a prospectively maintained database of all patients undergoing ETSS and EETSS, performed by a single neurosurgeon (MJ) between July 2006 and June 2015 at two institutions.

Demographic details including age, sex, body mass index (BMI), relevant medical history such as previous surgery or radiotherapy as well as surgery specific details such as tumour type, presence of an intra-operative CSF leak and the method of skull base repair at the conclusion of the procedure were collected for each patient. Intra-operative CSF leaks were graded as minor, moderate or major according to the classification system proposed by Esposito et al [10]. The presence or absence of a CSF leak post-operatively was recorded for each patient.

Pituitary adenomas were classified as microadenomas, macroadenomas or giant adenomas on the basis of a maximal diameter of < 10 mm, > 10 mm or > 40 mm, respectively. For pituitary adenomas, the extent of resection of tumour was assessed on a post-operative MRI scan 3 months after surgery by 2 neuroradiologists (MB, SL) and dichotomised into subtotal resection or gross total resection. Skull base repair following tumour resection was performed in the early part of the series using an autologous fat graft secured with tissue glue. In the latter part of the series, a vascularised nasoseptal flap secured with tissue glue was used. When a major intra-operative CSF leak was encountered, a multilayered closure using fascia lata placed intradurally, pedicled nasoseptal flap and tissue glue was used. Prophylactic lumbar drains were not used.

Post-operative CSF leaks were diagnosed clinically by the tilt test. Treatment of post-operative CSF leak consisted of lumbar CSF drainage or surgical re-exploration and CSF leak repair.

Descriptive statistics are presented as mean, with the standard deviation and range presented in parentheses immediately afterwards. The Fisher's exact test or chi-squared test was used to assess for between group differences in categorical variables. The two-sided Student's *t* test was used to assess for between group differences in continuous variables. For the purposes of multivariate analysis, a multifactorial logistic regression analysis was performed. Statistical significance was considered at an alpha level of < 0.05. All statistical analysis was performed using SPSS version 25 (IBM Corporation, USA).

Results

During this study, 270 procedures were performed on 255 patients. Demographic data not including BMI, as well as data regarding previous surgery, tumour histology, method of repair and post-operative CSF leak were available for all patients. Data regarding patient BMI was missing for 42 procedures, and data regarding previous radiotherapy was missing for 3 procedures.

The overall rate of post-operative CSF leak was 24/270 procedures (9%). The majority of procedures was performed in adult patients, with a mean age at the time of surgery of 50.1 (± 18.7, 4–85). The mean BMI was 29.4 (± 5.96, 14.7–45.4). The demographic details of the patients are summarised in Table 1. There was no significant difference in age (44.3 ± 18.1, 13–79 vs 50.6 ± 18.6, 4–85 $p = 0.11$) or BMI (28.6 ± 5.7, 21.3–41.2 vs 29.4 ± 6.0, 14.7–45.4 $p = 0.55$) when patients who did and did not develop a post-operative CSF leak were compared. Patients were split into obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) categories, and the rate of post-operative CSF leak was not found to differ significantly between these groups (8/100 (8%) vs 14/128 (11%), $p = 0.46$).

The majority of procedures was performed for resection of a pituitary adenoma (205/270, 76%). The case breakdown is demonstrated in Fig. 1. When pituitary adenomas were considered in isolation, there was no difference in the rate of post-operative CSF leak following resection of microadenomas, macroadenomas or giant adenomas (4/31 (13%) vs 11/155 (7%) vs 2/19 (11%), $p = 0.53$). Data on the extent of resection were available for 171/205 pituitary adenomas. When the CSF leak rates of patients who underwent a gross total resection was compared with those who had a subtotal resection were analysed, no difference was identified (6/58 (10%) vs 9/113 (8%), $p = 0.626$).

Table 1 Patient characteristics at the time of surgery

Variable	Value
Mean age ± SD	50.1 ± 18.7
Paediatric, *n* (%)	18 (7)
Adult, *n* (%)	252 (93)
Female, *n* (%)	129 (48)
Mean BMI ± SD	29.4 ± 6.0
Non-obese, *n* (%)	128 (56)
Obese, *n* (%)	100 (44)

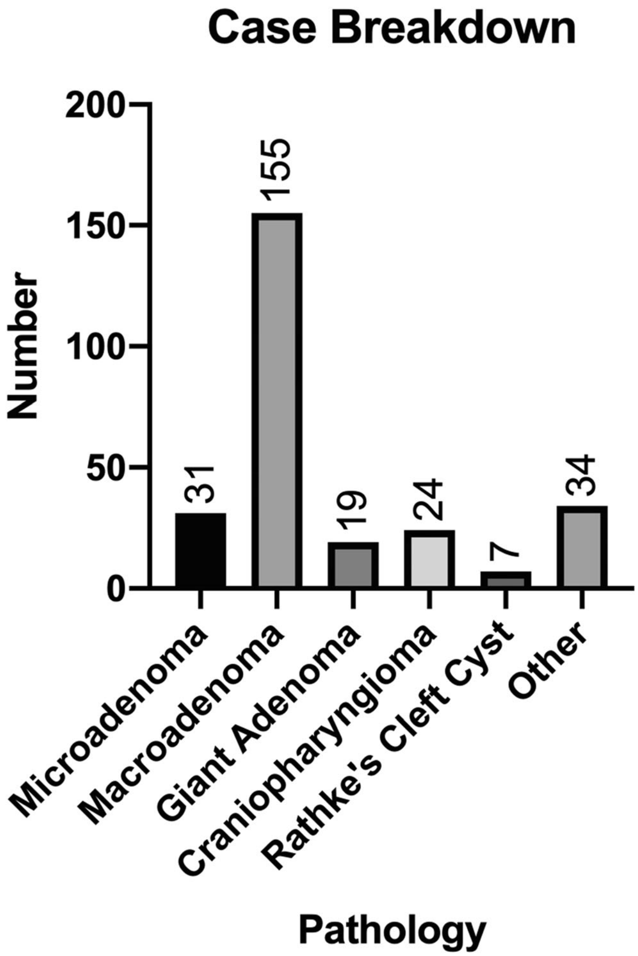

Fig. 1 Column graph demonstrating the breakdown of cases in this study. The majority of cases were pituitary adenomas, with macroadenomas making up the majority of pituitary tumours resected

However, when craniopharyngiomas were compared with all other pathology, the rate of post-operative CSF leak was higher in patients in the craniopharyngioma group compared with those with other pathology (5/24 (21%) vs 19/246 (8%), $p = 0.031$). Patients who had undergone previous transsphenoidal surgery had a higher rate of post-operative CSF leak than those who were having their first operation (6/33 (18%) vs 22/237 (8%), $p = 0.045$). This was not the case for patients who had previously had therapeutic irradiation to their tumour (2/19 (11%) vs 22/248 (9%), $p = 0.808$).

When hormonally active tumours were considered, there was no significant increase in the rate of post-operative CSF leak in patients with acromegaly, but in patients with resection of a microadenoma causing Cushing's disease, a statistically significant increase in the rate of post-operative CSF leak was evident. 6/26 (23%) of patients with Cushing's disease experienced a post-operative CSF leak comapred with 18/244 (7%) patients without Cushing's disease (p=0.007).

In terms of intra-operative factors influencing the development of post-operative CSF leak, we found that an intra-operative CSF leak was associated with an increased rate of this complication (18/109 (17%) vs 6/161 (4%), $p = <0.001$). However, when we separated the intra-operative leaks into minor/moderate and major categories, there was no significant difference between these groups in terms of the rate of post-operative CSF leak (12/53 (23%) vs 6/56 (11%), $p = 0.220$).

The use of a vascularised nasoseptal flap was associated with a lower rate of post-operative CSF leak than when a nasoseptal flap was not used (4/117 (3%) vs 20/153 (13%), $p = 0.005$). Furthermore, when the series was divided into three separate series, arranged chronologically, it was clear that increasing surgical experience had a significant impact on the rate of post-operative CSF leak: it occurred in 19 of the first 90 cases (21%), 4 of the second 90 cases (4%) and 1 of the last 90 cases in the series (1%) ($p = <0.001$) (Fig. 2).

All of the factors that were found to be predictive of post-operative CSF leak on univariate analysis were entered into a multifactorial logistic regression model (Table 2). On multivariate analysis, resection of a tumour associated with Cushing's disease (OR 4.229, 95% CI 1.56–13.32, $p = 0.01$) and intra-operative CSF leak (OR 4.56, 95% CI 1.56–13.32, $p = 0.006$) was associated with an increased rate of post-

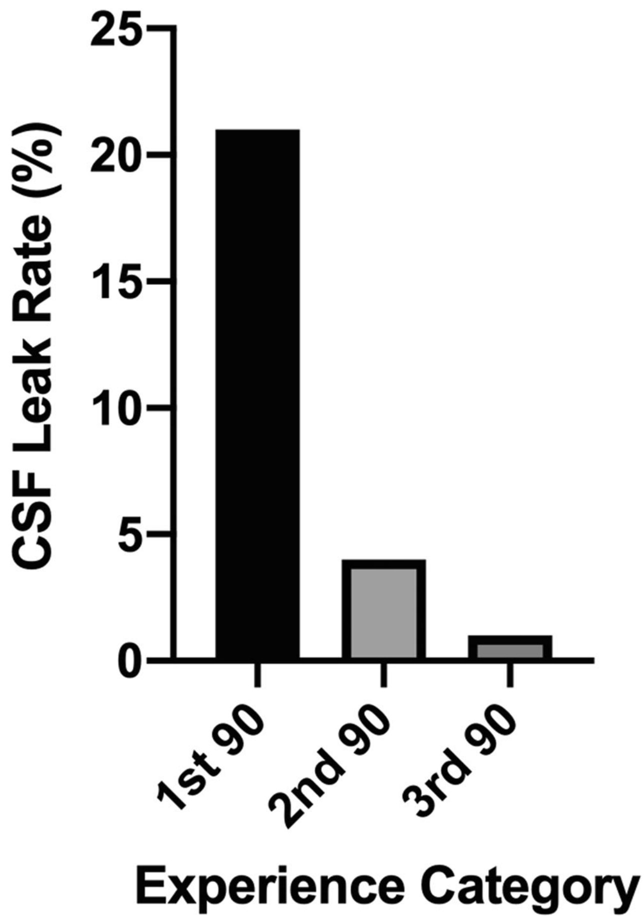

Fig. 2 Column graph demonstrating the proportion of procedures complicated by a post-operative CSF leak. This complication became significantly less frequent as the experience of the surgeon increased

Table 2 Multifactorial logistic regression analysis of factors predictive of post-operative CSF leak

Factor	Odds ratio for CSF leak (95% CI)	Significance
Previous surgery	1.49 (0.48–5.10)	0.523
Nasoseptal flap	0.84 (0.25–3.92)	0.769
Craniopharyngioma	4.229 (1.56–13.32)	0.057
Cushing's disease	**5.79 (1.53–21.95)**	**0.010**
Intra-operative CSF leak	**4.56 (1.56–13.32)**	**0.006**
Surgical experience	**0.14 (0.04–0.46)**	**0.001**

operative CSF leak. Increasing surgical experience (OR 0.14, 95% CI 0.04–0.46, $p = 0.001$) was associated with a decreased rate of post-operative CSF leak.

Discussion

In this series of ETSS and EETSS, we report an overall post-operative CSF leak rate of 9% (24/270), although the incidence of this complication decreased significantly as the series progressed and the experience of the surgeon increased. Our data also demonstrate that intra-operative CSF leak and resection of pituitary adenomas associated with Cushing's disease were associated with a statistically significant increase in the rate of post-operative CSF leak (Table 2).

The rate of CSF leak in this series is higher than that reported in large series of ETSS for resection of pituitary adenomas: in a large series of 624 ETSS for pituitary adenoma, Berker et al. reported a post-operative CSF leak rate of 1.3% [2]. Similarly, Cappabianca et al., in a highly cited series of 146 patients with pituitary adenoma, reported a CSF leak rate of 2.05% [3]. Although these figures are significantly lower than the post-operative CSF leak we report in our series, this discrepancy must be considered alongside the fact that these series are solely comprised of pituitary adenomas: 24% of the cases in our series were for non-adenomatous pathology, which are associated with a higher risk of post-operative CSF leak [23]. Moreover, EETSS for skull base pathology is associated with a higher rate of CSF leak than more standard transsphenoidal approaches to pituitary tumours: in a series of 800 patients treated using purely endoscopic endonasal techniques in a high volume centre, the authors reported a combined CSF leak rate of 15.9% when EETSS for extrasellar pathology was combined with standard ETSS, which increased to 19.4% when only expanded approaches were analysed. Interestingly, the authors reported a CSF leak rate of 10% for resection of pituitary adenomas [20]. When analysing our overall CSF leak rate, it should also be borne in mind that this series is consecutive and begins with the senior author's first case as an independent practitioner; the series reported by Cappabianca et al. and Berker et al. do not make clear where on the learning curve the operating surgeon(s) were when the data was collected. Moreover, in a wide ranging national study of pituitary surgeons, Ciric et al. demonstrated a strong inverse correlation between surgical experience and the incidence of post-operative complications, including CSF leak [6]. Our own data makes clear that surgical experience is a highly significant contributor to the rate of post-operative CSF leak: we report an OR of 0.14 (95% CI 0.04–0.46, $p = 0.001$) for post-operative CSF leak as surgical experience increased from the first 90 to the third 90 cases in this series.

Following its introduction in 2006, the vascularised nasoseptal flap has been successfully utilised in skull base repair following ETSS and EETSS, with numerous publications highlighting a decreased rate of post-operative CSF leak when this closure technique is used [14, 16, 26]. We also found this to be the case in our series: the rate of post-operative CSF leak following procedures where the nasoseptal flap was not used was significantly higher than when this technique was used (20/153 (13%) vs 4/117 (3%), $p =$ 0.005). Having been found to be associated with a decreased rate of post-operative CSF leak, nasoseptal flap use was added to a multifactorial logistic regression model (Table 2) where it was found not to have a statistically significant association with post-operative CSF leak. Nasoseptal flap use was strongly correlated with surgical experience: 4 of the first 90 (4.4%) cases were closed using a nasoseptal flap, whereas 75 of the third 90 cases were closed using this method (83.3%, $p = <0.001$). The strong correlation between increasing surgical experience and nasoseptal flap use makes it difficult to separate the differential contributions of these factors to the decreased rate of post-operative CSF leak observed as the series progressed, but on multivariate analysis, increasing experience was demonstrated to have a greater impact on decreasing the odds of a post-operative CSF leak.

Data from a number of longitudinal series have highlighted an increased rate of CSF leak following ETSS in obese compared with non-obese patients [8, 17, 27]. This was not the case in our series, where there was no difference in the rate of post-operative CSF leak in obese (8%) vs non-obese patients (11%). There was no observed difference in the mean BMI of patients that did vs. those that did not develop a post-operative CSF leak (28.6 ± 5.7, 21.3–41.2 vs 29.4 ± 6.0, 14.7–45.4 $p =$ 0.55). In a recent randomised control trial examining the role of lumbar drain insertion following EETSS for skull base tumours, the authors also reported no impact of BMI on the rate of post-operative CSF leak [29]. It is, however, mechanistically plausible that obesity would increase the rate of post-operative CSF leak and obesity is demonstrably associated with spontaneous, non-iatrogenic CSF leak [9]. Although our data did not demonstrate an association between obesity and CSF leak, we do report an increased rate of post-operative

CSF leak in patients who had Cushing's disease. When compared with all of the other procedures in the series, those that were performed for Cushing's disease were associated with an increased rate of post-operative CSF leak (6/26, (23%) vs 18/244 (7%), $p = 0.007$). In a number of studies examining ETSS for Cushing's disease specifically, the rate of post-operative CSF leak ranged from 0 to 1% [5, 15, 24]. Moreover, in a number of studies designed to identify factors associated with an increased risk of post-operative CSF leak following ETSS, none have identified Cushing's disease as a risk factor [12, 17, 23]. The reason for our higher CSF leak rate in Cushing's disease is not clear. It may be due to the small number of Cushing's disease cases in our series. Another factor may be poor healing in patients with Cushing's disease, but the low rate of CSF leak reported in other published series does not support this theory. Another factor may have been the method of skull base repair. All 6 patients with Cushing's disease who had post-operative CSF leak were repaired with autologous fat graft and tissue glue rather than nasoseptal flap. However, this theory is not supported by previous published series which have demonstrated low CSF leak rates in Cushing's disease without the use of nasoseptal flap [24]. Therefore, the most likely explanation may be that all 6 post-operative CSF leaks in our patients with Cushing's disease occurred during the first 90 cases in our series, when the surgeon was less experienced. This lack of experience may be more relevant to surgery for Cushing's disease than for other pituitary adenomas. Surgery for Cushing's disease can be difficult, and the surgeon's desire to remove the tumour in its entirety to achieve remission may lead to a higher rate of intra-operative CSF leak due to arachnoid tears. A small CSF leak may go unnoticed by a less experienced neurosurgeon. It is likely that our higher CSF leak rate in Cushing's disease compared with published large series is that our series includes the very early part of the author's experience.

Craniopharyngiomas, although histologically benign, are locally invasive tumours that have a propensity for growth into the suprasellar cistern and third ventricle [18, 21]. Given that they are commonly located within the subarachnoid space or within the third ventricle, it is not surprising that these tumours are associated with a high rate of post-operative CSF leak: a series of 64 patients from a large academic centre reported a CSF leak rate of 23.4% [21]. CSF leak rates of 20–30% have also been reported in other series, mirroring our results [7, 11]. However, in a series of 800 patients with a wide variety of pathology treated with EETSS, Kassam et al. observed that the CSF leak rate for craniopharyngiomas was 58% prior to the introduction of a vascularised nasoseptal flap closure, compared with 5.6% after this technique was adopted [20]. A similar trend was observed in our series: 2/8 (25%) procedures for resection of craniopharyngioma when a nasoseptal flap was not used for skull base repair were complicated by a CSF leak, compared with 3/16 (19%) when a nasoseptal flap was utilised, although this difference was not statistically significant and the absolute number of cases in this group was relatively small.

Intra-operative CSF leak was a strong predictor of post-operative CSF leak in this series, with an OR of 4.56 (95% CI 1.56–13.32, $p = 0.006$) on multivariate analysis. Overall, intra-operative CSF leak was encountered in 109/270 (40%) of procedures. Recognising that intra-operative CSF leak is a strong predictor of post-operative leak, a randomised control trial by Zwagerman et al. explored whether the use of prophylactic lumbar drainage following an expanded endoscopic endonasal approach to skull base pathology involving a large dural defect and/or arachnoid dissection/entry into the ventricular system. The authors reported a CSF leak rate of 21.2% in those without a lumbar drain compared with 8.2% in those with a prophylactic lumbar drain. These results prompted the authors to recommend prophylactic lumbar drain insertion in patients with anterior or posterior skull base pathology following an extended endonasal approach, but they did not go as far as to recommend this in patients with sellar/suprasellar pathology due to a lack of effect in this subgroup [29].

The primary limitation of our study is that data regarding BMI and radiotherapy were missing for 41 and 3 patients, respectively. Although this impacts on the quality of our dataset, these data points were available for the vast majority of patients, and the rate of post-operative CSF leak in those patients for whom BMI was not available did not differ significantly from that for whom information regarding BMI was available (2/42, 5% vs 22/228, 10%, $p = 0.306$). We included a wide variety of pathologies in this series, and the small numbers of some of these decrease the power of statistical tests and may limit the specific conclusions that can be drawn regarding these smaller groups.

This large series encompasses a wide range of pathologies, including non-pituitary disease, and is reflective of the varied practice of the modern endoscopic skull base surgeon, increasing the generalisability of our results. The results facilitate the prospective identification of patients at higher risk of post-operative CSF leak following endoscopic endonasal surgery. Equipped with this information, further measures can be taken in such patients in an attempt to prevent this complication, such as particularly fastidious, multilayered skull base repair.

Conclusion

Increasing surgical experience, in combination with vascularised pedicle closure techniques, demonstrably reduces the rate of post-operative CSF leak following endoscopic endonasal surgery for skull base and sellar pathology. Increased extent of resection of pituitary adenomas did not impact on post-operative CSF leak rate, and concern about increased risk of post-operative CSF leak should not limit aggressive tumour resection, when appropriate. Patients with an intra-operative CSF leak or those undergoing surgery for Cushing's disease may be at an increased risk for this complication, and meticulous skull base repair and close observation are recommended for these patients. The role of prophylactic lumbar drainage in the setting of an observed intra-operative CSF leak is unclear and requires further investigation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the institutional audit boards of the Walton Centre for Neurology and Neurosurgery, Liverpool, UK and Beaumont Hospital, Dublin, Ireland.

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