A phenomenon not to be missed: delayed postoperative cerebrospinal fluid rhinorrhea following no identifiable intraoperative leak in sellar surgery

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Dear Editor:

The endonasal endoscopic approach (EEA) to skull base pathologies has gained widespread adoption, with prevention of postoperative cerebrospinal fluid (CSF) leaks being a key goal. Yet there is a minority of patients who do not have an identified intraoperative CSF leak following resection but go on to develop a postoperative CSF leak that requires intervention, which we have termed delayed CSF leaks. These events are generally very rare and anecdotally reported, with limited published data [1–3]. Theoretically, there are several proposed etiologies for delayed CSF leaks apart from missed intraoperative CSF leak. Previously reported features in these patients have included excessive postoperative straining due to emesis, coughing, or noncompliance with postoperative restrictions, which may increase intracranial pressure (ICP), thereby rupturing an already thinned diaphragma sella. Due to the rarity of delayed CSF leaks, this multicenter study was conducted to analyze patient factors and presentation, clinicopathologic characteristics, and management outcomes.

Briefly, patients were identified from case logs who underwent EEA for sellar pathologies across 9 tertiary academic skull base surgery programs. Inclusion criteria were patients who underwent transnasal endoscopic transsphenoidal surgery for sellar pathologies with no identified intraoperative CSF leaks (Esposito grade 0) [4] but subsequently developed CSF leaks postoperatively (Supplemental material).

Out of 3271 sellar EEA cases across the collection period at all institutions, 26 (0.79%) patients with delayed postoperative CSF leaks were identified. Among cases known to have no intraoperative CSF leak, the delayed leak rate was 1.17%. Time to presentation of leak from index surgery was 7.0 ± 12.8 days and the median time was 3 days (interquartile range: 2-7 days). All cases were successfully repaired secondarily. Table 1 lists baseline patient, clinicopathologic, and surgical characteristics, while

Table 1. Baseline patient characteristics and clinicopathologic data.

Number of patients		26
Age (years) (mean (SD))		47.4 (14.4)
Sex (%)	Female	15 (57.7)
	Male	11 (42.3)
BMI (mean (SD))		29.6 (10.4)
Obese (%)	No	14 (53.8)
	Yes	12 (46.2)
HTN (%)	No	15 (57.7)
	Yes	11 (42.3)
DM (%)	No	22 (84.6)
	Yes	4 (15.4)
OSA (%)	No	20 (76.9)
	Yes	6 (23.1)
Pathology (%)	Non-functioning/unspecified pituitary adenoma	7 (26.9)
	Rathke's cleft cyst	8 (30.8)
	Functioning pituitary adenoma	11 (42.3)
Prior surgery? (%)	No	25 (96.2)
	Yes	1 (3.8)
Prior XRT? (%)	No	24 (92.3)
	NA	2 (7.7)
Prior head trauma? (%)	No	24 (92.3)
	NA	2 (7.7)
Size (mm) (mean (SD))		23.4 (10.5)
Laterality (%)	Bilateral	21 (80.8)
	Left	2 (7.7)
	Right	3 (11.5)
Suprasellar involvement? (%	No	8 (30.8)
	Yes	18 (69.2)
Cavernous involvement? (%)	No	13 (50.0)
	Yes	13 (50.0)
Superior clival involvement? (%)	No	24 (92.3)
	Yes	2 (7.7)
Sphenoid involvement? (%)	No	21 (80.8)
	Yes	5 (19.2)
Extent of approach? (%)	Transsellar	23 (100.0)
Skull base defect (mm) (mean (SD))		18.1 (5.5)
Native pituitary identified? (%)	No	5 (19.2)
	Yes	19 (73.1)
	NA	2 (7.7)
Diaphragm Descended? (%)	No	5 (19.2)
	Yes	15 (57.7)
Diaphragm Thin? (%)	No	9 (34.6)
	Yes	11 (42.3)
Diaphragm herniated into sphenoid? (%)	No	17 (65.4)
	Yes	3 (11.5)
Rathke's Cleft Cysts		
Marsupialized? (%)	Yes	8 (30.8)
Cyst wall removed? (%)	No	5 (19.2)
	Yes	3 (11.5)
Stented? (%)	No	6 (23.1)
	Yes	2 (7.7)
Stent Type (%)	Silastic	2 (7.7)
FMG vs NSF (%)	FMG	2 (7.7)
	None	1 (3.8)
	NSF	3 (11.5)
Initial Reconstruction (%)	FMG	6 (23.1)
	None	16 (61.5)
	NSF	4 (15.4)
Presentation of Leak		
POD (mean (SD))		7.0 (12.8)
Location (%)	Inpatient	18 (69.2)
	Outpatient	8 (30.8)
Rhinorrhea? (%)	No	3 (11.5)
	Yes	23 (88.5)
Salty/metallic taste? (%)	No	13 (50.0)
	Yes	6 (23.1)
Fever? (%)	No	20 (76.9)
	Yes	6 (23.1)
Headache? (%)	No	15 (57.7)
	Yes	10 (38.5)
Meningitis? (%)	No	23 (88.5)
	Yes	3 (11.5)
Inciting Event?	No	16 (61.5)
	Yes	10 (38.5)
Nausea/vomiting? (%)	No	22 (84.6)
	Yes	4 (15.4)
Stress-related activities? (%)	No	21 (80.8)
	Yes	4 (15.4)
	No	17 (65.4)
Cough? (%)	Yes	3 (11.5)
	No	18 (69.2)
Sneeze? (%)	Yes	2 (7.7)
Delayed Leak CSF Grade (1-3) (%)	0	0 (0)
	1	5 (19.2)
	2	8 (30.8)
	3	3 (11.5)
Defect location (%)	Diaphragm	16 (61.5)
	None identified	10 (38.5)
Intervention Type (%)	Bedrest	1 (3.8)
	Lumbar Drain	5 (19.2)
	Surgical Repair	14 (53.8)
	Repair, Lumbar Drain	6 (23.1)
POD Intervention (mean (SD))		7.9 (13.0)
Outcome (%)	Re-leak/Revision → Resolution	1 (3.8)
	Resolution	25 (96.2)
Follow up (months) (mean (SD))		35.0 (27.9)

Abbreviations: SD, standard deviation; RCC, Rathke's cleft cyst; FMG, free mucosal graft; NSF, nasoseptal flap. Not all variables were available or applicable for the reported cases. Percentages are based on the total number of cases.

Table 2 lists specific presentation, inciting events, and outcomes for each patient.

This report represents the largest series of systematically reported delayed postoperative CSF leaks. The majority of the patients had suprasellar extension of pathology; presumably, as the diaphragma sella becomes distended over the lesion in

Table 2. Clinical case summaries for all 26 patients.

Case #	Age	Sex	BMI	Pathology	Suprasellar Extension	Skull base defect (mm)	Initial Reconstruction	POD Leak	Any inciting event?	Mng	Intervention	POD Tx	Outcome
1	53	F	39.7	RCC	Yes	21	NSF	4	Yes	No	Repair: Duragen, NSF	8	Resolved
2	32	F	37	fPA	No	20	FMG	2	Yes	No	Repair: Duragen plus, NSF	2	Resolved
3	42	M	28.4	fPA	Yes	25	DuraMatrix/FMG	6	No	No	Repair: abd fat, plate, NSF	7	Resolved
4	35	F	24.6	fPA	Yes	25	FMG	1	No	No	Repair: abd fat, plate, NSF	1	Resolved
5	77	F	43.5	RCC	Yes	20	FMG	1	Yes	No	Repair: abd fat, DuraMatrix, NSF	1	Resolved
6	69	M	28	nfPA	Yes	25	FMG	8	No	Yes	Repair: b/l MT flaps, DuraSeal	13	Resolved
7	53	F	46	nfPA	Yes	25	None	5	Yes	No	Repair, LD: abd fat, NSF	7	Resolved
8	54	M	26	RCC	Yes	20	None	1	Yes	No	Repair: abd fat, plate, NSF	1	Resolved
9	30	F	21.3	fPA	No		None*	1	No	No	LD	2	Resolved
10	50	M	13.8	fPA	No		None*	2	No	No	Repair, LD	4	Resolved
11	27	M	12.7	fPA	Yes		None*	3	No	Yes	Repair	4	Resolved
12	25	F	13.3	RCC	Yes		NSF	6	No	No	LD	6	Resolved
13	47	M	12.6	nfPA	Yes		None*	3	No	No	LD	2	Resolved
14	41	F	22.7	nfPA	Yes		None*	1	No	No	Repair, LD	2	Resolved
15	52	M	40.4	fPA	Yes	15	NSF	29	No	No	Repair	31	Resolved
16	30	F	40.7	fPA	Yes		NSF	63	Yes	No	Repair, LD	64	Re-leak/ re-operation → Resolved
17	54	F	30.8	PA	Yes		None	2	Yes	No	Repair	2	Resolved
18	66	F	31.8	RCC	Yes		None	5	No	No	Repair, LD	5	Resolved
19	62	M	43.1	RCC	Yes		None	14	No	No	Repair	14	Resolved
20	52	F	26	PA	No		None	7	Yes	No	LD	7	Resolved
21	65	F	41	PA	No		None	2	No	No	Bedrest	2	Resolved
22	55	M	21	RCC	No		None	7	No	Yes	Repair	8	Resolved
23	27	F	26	fPA	Yes	15	Fat/ DuraGen	2	Yes	No	LD	2	Resolved
24	31	F	42	fPA	No	13	None*	3	Yes	No	Repair	3	Resolved
25	47	M	25	fPA	Yes	13	Fat/FMG	3	No	No	Repair, LD	7	Resolved
26	57	M	33	RCC	No	12	None	1	No	No	Repair	1	Resolved

Abbreviations: BMI, body mass index; POD, postoperative day; Mng, meningitis; Tx, treatment; PA, pituitary adenoma; RCC, Rathke's cleft cyst; NSF, nasoseptal flap; FMG, free mucosal graft; LD, lumbar drain; MT, middle turbinate; fPA, functioning pituitary adenoma; nfPA, non-functioning pituitary adenoma; PA, pituitary adenoma. Black cells indicate data were not available. * indicates Surgicel/Gelfoam placed. DuraMatrix (Stryker Corporation, Kalamazoo, MI). Surgicel (Johnson & Johnson, New Brunswick, NJ). Gelfoam (Pfizer, New York, NY). DuraGen (Integra LifeSciences, Princeton, NJ)

the suprasellar space, it thins and becomes more susceptible to breaches with rapid ICP changes (e.g., straining, retching). Indeed, in 10 cases (38.5%) there was an identifiable event, such as emesis, straining, and exertion, that precipitated a CSF leak. This may also be a factor after Rathke's cleft cyst (RCC) surgery. In this series, all RCC patients had cysts marsupialized into the sphenoid sinus to prevent restenosis/recurrence [5–7]. After the cyst fluid is decompressed, the thinned dura may be prone to rupture, possibly due to traumatic irritation by stent material, tearing over bony edges, or postoperative ICP shifts. However, it is also possible that small unidentified CSF leaks occurred intraoperatively that only become apparent postoperatively.

There are proposed strategies to mitigate the risk of delayed CSF leaks. First, careful examination of the defect and surgical field after surgery to rule out subtle intraoperative CSF leak is critically important. Meticulous hemostasis and irrigation to

clean the field, Valsalva manuevers, and giving time for subtle leaks to declare (i.e., clear fluid pooling), may allow for identification of any subtle leaks. Intraoperative fluorescein may also be considered when concerned for a subtle leak, though this requires lumbar drain placement and was not routinely utilized in any cases. Second, consideration should be given to prophylactic onlay coverage of the bony defect with grafts or flap and/or reduction and obliteration of the sella (e.g., collagen matrix) to prevent trauma to the diaphragma from bony edges, particularly in cases where the diaphragma has thinned and herniated inferiorly. However, this practice is counter to the goal of RCC marsupialization, and the risks of delayed leaks and cyst recurrence must be balanced. Finally, implementing strict postoperative precautions and protocols (e.g., dedicated counseling/education, standard antiemetics) is important for limiting Valsalva and ICP spikes, though this requires further study [8,9].

List of abbreviations

BMI, body-mass index; CSF, cerebrospinal fluid; EEA, endoscopic endonasal approach; FMG, free mucosal graft; ICP, intracranial pressure; LD, lumbar drain; NSF, nasoseptal flap.

Authorship contribution

Conception and design: ECK.
Acquisition of data: RSK, JGE, AA, KPA, PF, DP, JR, NDA, PSB, MSB, JRC, JCF, PAG, MSG, AAH, FPKH, AM, JNP, PP, CHS, BAT, EWW, MBW, GZ, GAZ, ECK.
Analysis and interpretation of data: RSK, JGE, AA, ECK.
Drafting of the manuscript: RSK, JGE, AA, ECK.
Critical revision of the manuscript: RSK, JGE, AA, KPA, PF, DP, JR, NDA, PSB, MSB, JRC, JCF, PAG, MSG, AAH, FPKH, AM, JNP, PP, CHS, BAT, EWW, MBW, GZ, GAZ, ECK.
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Conflict of interest

The authors declare no relevant conflicts of interest.

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SUPPLEMENTARY MATERIAL

Materials and methods

Patient selection

Patients who underwent endonasal endoscopic surgery (EEA) for sellar pathologies were retrospectively reviewed across 9 tertiary academic medical centers with skull base surgery expertise including Henry Ford Health System, Detroit, MI; Rush University Medical Center, Chicago, IL; Stanford Hospital, Stanford, CA; University of California Irvine, Orange, CA; University of California, Los Angeles, Los Angeles, CA; University of Pennsylvania, Philadelphia, PA; University of Pittsburgh Medical Center, Pittsburgh, PA; University of Southern California, Los Angeles, CA; University of Texas Southwestern Medical Center, Dallas, TX. The data collection spanned from inception of the respective institution's skull base program through December 31, 2021. Institutional Review Board approval at all participating sites was obtained. Inclusion criteria were patients who underwent EEA for sellar or suprasellar pathologies with no identified intraoperative CSF leaks (Esposito grade 0)3 but subsequently developed CSF leaks postoperatively. Accordingly, exclusion criteria included confirmed intraoperative CSF leaks, open or combined open and endoscopic surgeries, and patients without operative or postoperative records available for review.

Data collection, variables and study outcomes

Pre-, intra-, and postoperative variables were collected in standard fashion for all included patients. Preoperative variables included demographic information, body-mass index (BMI), comorbidities, and pathologic data (tumor pathology, lesion size [single greatest dimension], cavernous sinus extension, suprasellar involvement). Although ICP was not routinely measured, no patients had a documented history of elevated ICP. Operative reports from the index tumor resection surgery were reviewed to determine whether the diaphragma sella was thinned or descended after resection (based on surgeon documentation), method of primary reconstruction at the time of index surgery, and any other intraoperative complications. For Rathke's cleft cysts, it was noted if the cyst was attempted to be marsupialized or if the cyst wall was removed, and if the cyst cavity was stented and stent material used. The clinical presentation of the postoperative leak was recorded including defect location; presence of rhinorrhea, fever, headache, and meningitis; time to postoperative CSF leak presentation following index surgery; presence of an inciting event prompting CSF leak; secondary management strategy; and outcome of secondary intervention. Stress-related activities were defined as any physical activity which resulted in increased ICP (e.g., Valsalva, coughing, nose blowing, heavy lifting). Length of follow-up was also noted.

Statistical analysis

Descriptive statistics were calculated to summarize patient data using Excel (Microsoft Corporation, Redmond, WA) and R (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria) in RStudio (version 1.4.1717, RStudio, Boston, MA). A value of $p < 0.05$ was considered statistically significant.

Treatment outcomes of delayed postoperative leaks

Management of the delayed postoperative CSF leaks followed standard CSF leak reconstructive paradigms. The median time to leak detection was 3 days, suggesting that delayed postoperative CSF leaks generally occurred in the immediate postoperative period, although there was one patient who developed a CSF leak 2 months after surgery. In most cases, patients required endoscopic re-exploration and repair. Given that the size of the defect is relatively small compared to other CSF leaks, CSF diversion via lumbar drain to allow the defect to close may be considered. However, the associated risks of lumbar drainage and prolonged bedrest, as well as pneumocephalus from lack of coverage of a dural defect, need to be considered carefully. In this series, all CSF leaks were able to be closed successfully whenever surgery was elected, although a few also resolved with conservative, nonsurgical measures alone.

Study limitations

There were several limitations to this work. Notably, the retrospective nature limits the details able to be abstracted from each individual patient chart. Due to the rarity of delayed postoperative leaks, this study was limited by a small sample size, which prevented more granular predictive analyses on patient subgroups. In addition, this work represents a convenience sample such that the true incidence of delayed postoperative leaks could not be determined, though we estimate it to be <1% overall. Our study pooled several different pathologic entities, but with a common surgical site (i.e., sellar). For most institutions, recording intracranial hypertension prior to surgery was not a part of routine care. The etiology of these delayed postoperative CSF leaks remains speculative and further research as to the exact mechanisms by which postoperative leaks can occur is needed. Furthermore, preoperative factors that may predispose patients to delayed postoperative leaks are also unknown from this current data set and deserve further scrutiny. Nevertheless, the data presented in the current study are the first of its kind to systematically study and report on this phenomenon, which is often discussed informally, anecdotally, and likely recognized by most skull base surgeons, but not well-studied.