Maltan *et al.*
The Egyptian Journal of Otolaryngology (2023) 39:133
https://doi.org/10.1186/s43163-023-00484-2

The Egyptian Journal of Otolaryngology

ORIGINAL ARTICLE Open Access

Predictors of failure of recurrent spontaneous CSF rhinorrhea repair: a prospective cohort study

Turkiya A. Maltan[1], Eman H. Salem[2*], Ahmed Hemdan Eldeeb[2], Waleed Moneir[2] and Yasser W. Khafagy[2]

Abstract

Background To identify and predict risk factors associated with recurrent spontaneous cerebrospinal fluid (CSF) rhinorrhea, a cohort study included a total of 37 adult patients with spontaneous CSF rhinorrhea were analyzed.

Results Over a 2-year period, 37 patients of spontaneous CSF leak with exclusion of other etiologies (traumatic, congenital) were enrolled: primary (non-recurrent) ($n = 20$) and secondary (recurrent) ($n = 17$), where 83.8% were females with an average body mass index (BMI) of 36.4 kg/m^2. Associated symptoms of high intracranial pressure (ICP) namely, blurred vision and unsteadiness (P-value = 0.006 and 0.01, respectively), multiparity (92.3%), and failure to localize the defect (17.6%) contributed to patients having more recurrence. Although the cribriform plate was detected frequently ($n = 29.4\%$), they were associated with lower recurrence compared to lateral recess of sphenoid (66.6% vs 20%).

Conclusion Direct endoscopic visualization and repair of skull base defects achieve a high success rate, but failure is still a possibility especially in spontaneous etiology of leaks. In a multiparous female, with high CSF pressure, lateral sphenoid recess, large size, or unidentified defect, the incidence of recurrence is much higher.

Level of evidence 4

Keywords Recurrent, Spontaneous, CSF leak, Endoscopic repair

Background

Spontaneous CSF rhinorrhearepresents a unique subset being the highest to recur of all other etiologies. Many studies have correlated it with benign intracranial hypertension (BIH) both clinically (headache, pulsatile tinnitus, vertigo, and visual disturbances) and radiologically (empty sella syndrome, dilated/tortuous optic nerve sheath, Meckel's cave, encephaloceles, and arachnoid pits). Therefore, for ideal management of spontaneous leaks, repair of the defect together with controlling the elevated intracranial pressure should be addressed [1–7].

Reviewing the literature shows paucity in studies reporting possible causes of recurrence in that specific category of patients. The purpose of the current study is to report our outcome with repair of spontaneous CSF leaks (both primary and recurrent) and to demonstrate how management of underlying intracranial hypertension improves the results.

Methods

A prospective cohort study included a total of 37 adult patients with spontaneous CSF rhinorrhea: 20 primary and 17 recurrent cases (of whom 3 were repaired in our institution and 14 were referred from an outside institution) over a period of 2 years. Specific operative details of

*Correspondence:
Eman H. Salem
emanhamdy7289@gmail.com
[1] Department of Otolaryngology-Head and Neck Surgery, Misurata University, Misurata, Libya
[2] Department of Otolaryngology-Head and Neck Surgery, Mansoura University, Mansoura 35511, Dakahlia, Egypt

the referred cases were thoroughly reviewed, and those who met the criteria of our repair techniques were only included. Patients with etiologies other than spontaneous rhinorrhea or pediatric group were excluded. An informed written consent and an ethical approval from Mansoura Faculty of Medicine Institutional Review Board (IRB) were obtained.

A detailed history was taken including all demographic data with special interest to body mass index (BMI). Neurological consultation with application of modified Dandy criteria was done to diagnose BIH together with fundus examination to assess the degree of papilloedema if present [8]. A non-contrast multislice high-resolution computed tomography (HRCT) scan was acquired at 1 mm thickness and a magnetic resonance imaging (MRI) of the nose and brain with IV contrast to exclude any intracranial pathology and identify signs of increased ICP in the heavy T2 cuts.

Under complete aseptic condition, preoperative measurement of CSF pressure was done, and a 0.5 ml of 10% fluorescein (10 mg) was slowly administered intrathecally. Then, the procedure was carried under general anesthesia. Based on the preoperative CT, location of the suspected leak was targeted and exposed using 4 mm 0°, 30°, and 45° endoscopes (Karl Storz GmbH 7 Co., Tuttlingen, Germany) following our previously proposed algorithm [9]. Meningocele/meningoencephalocele, if found, were cauterized and excised with bipolar forceps. The mucosa was taken off for at least 5 mm in all directions, and the bony margins were dissected from the dura to facilitate insertion of an underlay graft. The technique of repair did not differ significantly for patients undergoing primary or secondary repair. A standardized bilayer repair was performed using combination of hard (bone chip) and soft tissue grafts (middle turbinate, inferior turbinate graft, platelet-rich fibrin (PRF), fat, or fascia lata). The graft was further held in place with layers of Surgicel and Gelfoam. No nasal pack was needed based on our experience.

In patients with high *ICP* > 25-cm H2O, a single dose of 100 cc 25% mannitol infusion was administered in the recovery room. Intravenous antibiotics, cough sedative, stool softeners, and antiemetics were prescribed as required in the early postoperative period, and patient was discharged in day 2 postoperative. For long-term control of ICP, patients were maintained on acetazolamide (250-mg TID upgraded to 2000 mg daily as per needed), together with bumetanide (1 mg once daily) with monthly check of the electrolytes. Combination of both diuretics gives better response and less side effects than use of one diuretic in large dose for long period. A second fundus examination and CSF pressure measurement were done at 2-month interval to determine whether to continue medically or to insert a shunt (for pressures exceeding 40-cm H2O after neurosurgical consultation), and follow up was continued for at least 6 months. Of noted, recurrence was considered when a leak at the same site occurred after > 2 months of cessation of the leak or developed at a separate anatomic site, whereas failure was described when the patient leaks in less than 2 months.

Results

A total of 37 patients (2ry ($n = 17$), 1ry ($n = 20$)) of spontaneous CSF leak were endoscopically repaired by the senior author over a 2-year period. Mean age was 42.3 years, and 31 patients were females (83.8%) with an average BMI of 36.4 kg/m^2 (Table 1) None of the associated comorbidities (hypertension, diabetes, or hepatic disease) significantly correlated with recurrence except for number of parities after exclusion of male patients where 92.3% of the recurrent cases were multiparous versus

Table 1 Relation between demographic data among in both groups

	Recurrence ***N*** **= 17 (%)**	**No recurrence** ***N*** **= 20 (%)**	***p*-value**
Age (year)	44.47 ± 11.58	40.05 ± 11.17	0.246
BMI (kg/m^2)	33.8 ± 5.74	36.17 ± 8.75	0.346
CSF pressure	32.53 ± 8.48	29.65 ± 7.6	0.284
Sex			
Male	4 (23.5%)	2 (10%)	0.383
Female	13 (76.5%)	18 (90%)	
Marital status			
Not married	1 (5.9%)	2 (10%)	> 0.999
Married	16 (94.1%)	18 (90%)	
Smoking			
Nonsmoker	15 (88.2%)	20 (100%)	0.204
Current smoker	2 (11.8%)	0 (0%)	
No. of deliveries	*N* = 13	*N* = 18	
Nullipara	1 (7.7%)	4 (22.2%)	< 0.001**
Primipara	0 (0%)	9 (50%)	
Multipara	12 (92.3%)	5 (27.8%)	
Leakage side			
Right	10 (58.8%)	10 (50%)	0.919
Left	6 (35.2%)	8 (40%)	
Bilateral	1 (5.8%)	2 (10%)	
Headache	17 (100%)	15 (75%)	0. 05
Blurring of vision	15 (88.2%)	8 (40%)	0.006*
Unsteadiness	9 (52.9%)	2 (10%)	0.01*
Meningitis	2 (11.8%)	1 (5%)	0.584
COVID-19	2 (11.8%)	1 (5%)	0.999
Pneumocephalus	1 (5.9%)	0 (0%)	0.459

* $P < 0.05$ is statistically significant

27.8% in the 1ry group. Although headache was the most common symptom (86.5%), recurrence occurred more frequently in patients complaining of blurred vision or unsteadiness (*P*-value = 0.006 and 0.01, respectively). Previous history of meningitis was detected in two recurrent and one 1ry patients (11.8% vs 5%). Of note, 2 patients with 2ry leak and 3 patients in the 1ry group reported a recent COVID-19 infection within the last 6 months. After his 1ry repair, one patient had massive pneumocephalus operated outside our institution, which was managed conservatively and reported recurrence of the leak after 4 months. Different sites of defect were detected with the cribriform plate being the highest in both groups (35.1%) (Fig. 1). Also, one patient had a history of multiple defects (posterior table frontal sinus and lateral lamella) detected in the first surgery with recurrence occurring at one of them (lateral lamella). Three patients' defects were unidentified in their primary repair (performed in an outside institution ($n = 2$) or in our hospital ($n = 1$)); however, a definitive leak was identified in only two of them in the secondary procedure. Detect size ≥ 1 cm was considered large and found in 47% of recurrent and 5% of 1ry patients. The accuracy of CT scan to detect the exact site of leak was higher in the primary cases (85% vs 58.8%) (Fig. 2), whereas MRI findings of increased ICP (empty sella, meningocele, dilated optic nerve sheath) were noticed more with recurrence (53% vs 10%) (Fig. 3). The mean ICP was slightly higher in the recurrent group (32.53 vs 29.65-cm H2O) when measured intraoperatively. A logistic regression analysis demonstrates various factors that reached a statistical significance among the 2 groups as shown in Table 1. Overall, multiparity, increased BMI, high ICP, lateral recess defects, and unidentified sites were associated with an increase in recurrence. Meanwhile, a small size of defect < 1 cm was associated with decreased recurrence.

Acetazolamide and bumetanide were initiated immediate postoperatively in all patients for a minimum period of 6 months with possible deprescription after cessation if headache evolves. None of the patients after secondary repair underwent ventriculoperitoneal shunt (VPS) placement with a success rate of 100% after a mean of 8.2 months of follow-up. In the 17 recurrent patients, mean recurrence-free survival was 66.4 months (with 95% CI) (Fig. 4). Recurrence was detected either at the primary site, a different site, or an unidentified leak in 29.4%, 52.9%, and 17.6%, respectively (Table 2), and all had repeat transnasal endoscopic repair. Of those, 3

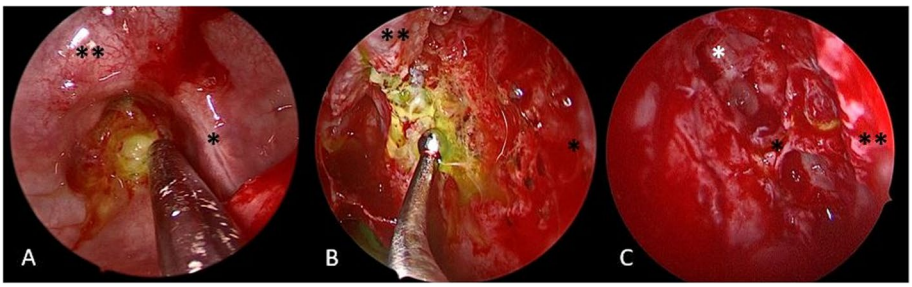

Fig. 1 **A** Defect in left clival recess. Note: sella (2 asterisks) and Vidian nerve (1 asterisk). **B** Defect in right posterior cribriform plate, nasal septum (1 asterisk), middle turbinate (2 asterisks). **C** Defect in right lateral lamella, middle turbinate (2 asterisks), anterior ethmoid artery (black asterisk), frontal ostium with no leak from the previously repaired defect (white asterisk)

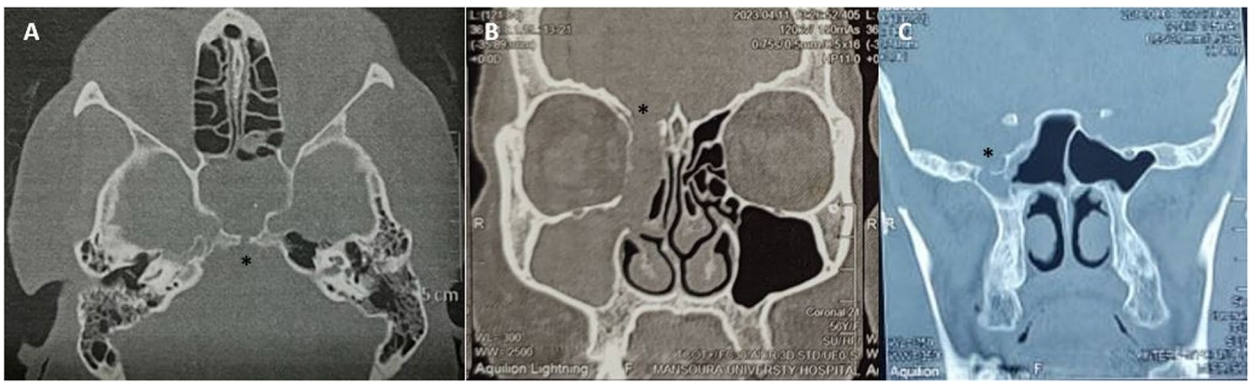

Fig. 2 **A** Defect in left clival recess (asterisk). **B** A large defect in right posterior fovea ethmoidalis (asterisk). **C** Defect in lateral recess of sphenoid (asterisk)

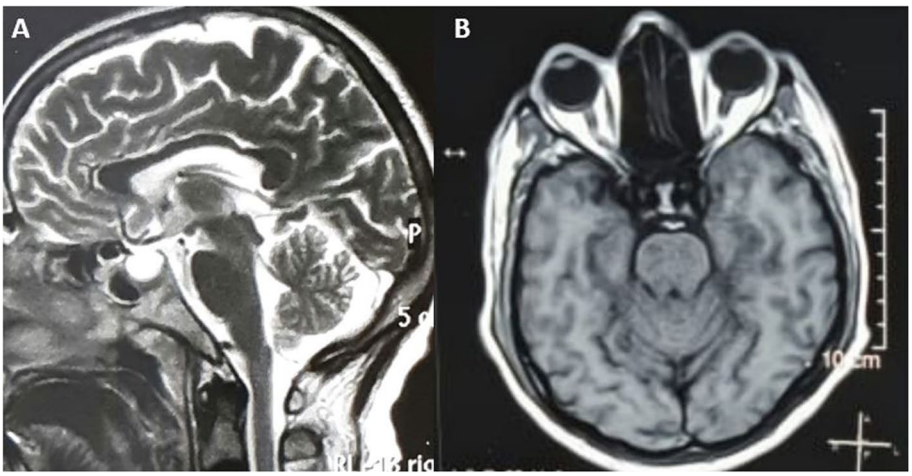

Fig. 3 Signs of increased ICP. **A** Complete empty sella (asterisk). **B** Dilated tortuous optic nerve sheath

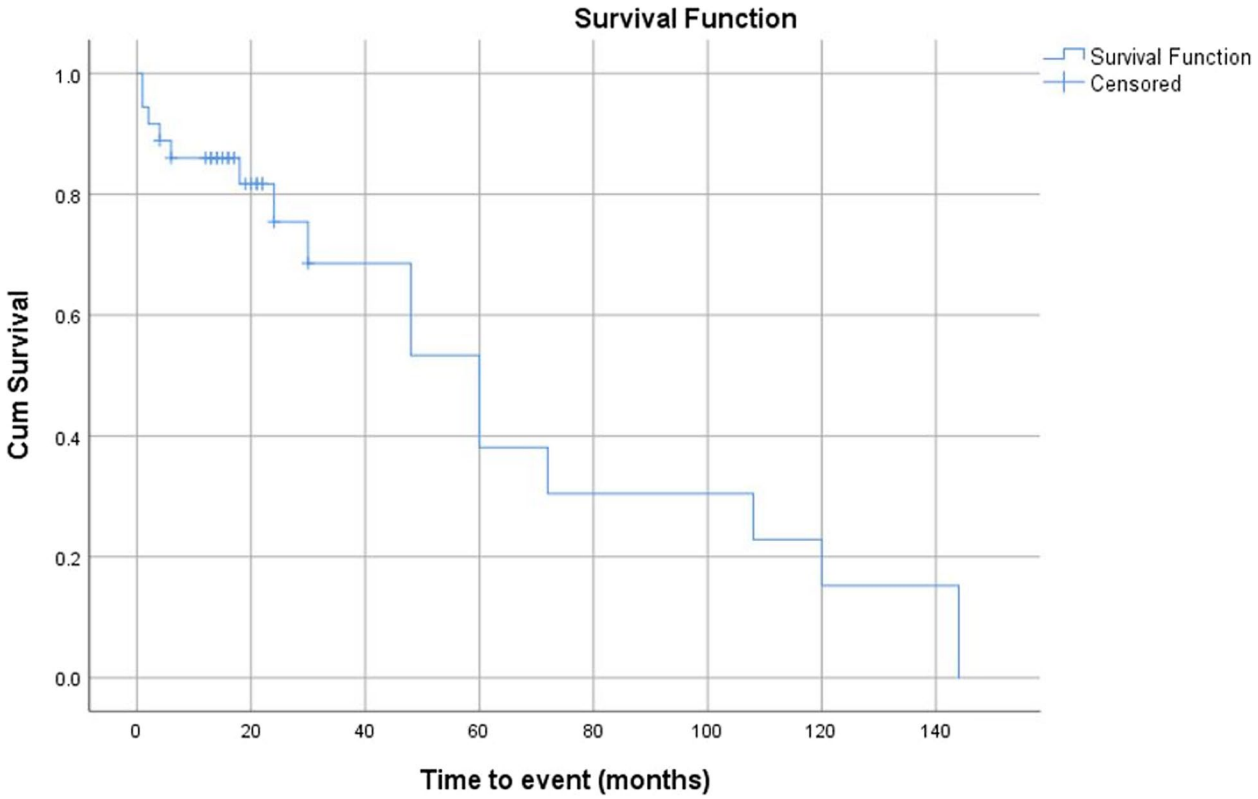

Fig. 4 Kaplan-Meier plot showing recurrence-free survival among studied patients

recurred within 2 months post-operatively. One of them linked recurrence to discontinuation of acetazolamide. Use of lumboperitoneal shunt (LPS) was employed in 2 cases with an ICP of 43 and 52-cm H2O at the recommendation of neurosurgical team, and none received a lumbar drain (LD). Table 3 represents a receiver operating characteristic (ROC) curve that is used to detect the positive predictive value (+PV) for probability of recurrence by assigning a cutoff point for suspected risk factor, where CSF pressure more than 39-cm H2O considered a cutoff point, and patient get recurrence by about 83.3. BMI more than 29.07 kg/m^2, number of parities > 1, and the size of defect > 1 cm increase the probability of recurrence by 60.7, 70.6, and 76.5, respectively.

Table 2 Logistic regression coefficients

Variable	Coefficient	AOR (95% *CI*)	*p*-value
Multiparity	24.188	31,957,908,905 (0)	0.998
BMI	0.669	1.95 (0.8–4.78)	0.14
CSF pressure	0.013	1.01 (0.89–1.15)	0.85
Unidentified site	21.583	2,362,463,547 (0)	> 0.999
Large size of defect	4.792	120.54 (0.41–35,791.21)	0.099

AOR Adjusted odds ratio, *CI* Confidence interval

Discussion

A total of 17 recurrent cases and 20 nonrecurrent patients were compared, and no specific factor reached statistical significance in demographic characteristics (age, sex, or comorbidities). However, the number of parities was statistically significant in the recurrent group. Female representation was 83.8% with an average BMI of 36.4 kg/m^2 consistent with BMI rates reported at 35.9 kg/m^2 and 36.2 kg/m^2 by Schlosser et al. and Woodworth et al., respectively [4, 10].

Mean ICP of the recurrent group was 32.53-cm H2O and 29.65-cm H2O for the nonrecurrent group. This is slightly higher than that reported by Schlosser et al. and Woodworth et al. at 26.5-cm H2O and 27-cm H2O, respectively [4, 10]. We believe that the most important factor predictive of recurrence is the increased ICP regardless of the preoperative reading which is sometimes misleading. The more reliable ways of suspecting high pressure were symptoms of blurred vision, unsteadiness, or MRI finding of empty sella+/− meningocele (*P*-value = 0.006, 0.01, 0.001, respectively). In accordance with Woodworth who found 3 patients had an ICP below 15-cm H2O, all had radiological evidence of elevated pressure (i.e., empty sella) and concluded reasons for low readings could be depleted CSF from excessive drainage, postoperative diuretics, or measurement of a single time point during natural daily fluctuations [10].

There are many reported methods of ICP management in the literature including medical treatments or permanent CSF diversion [11]. We routinely prescribed acetazolamide and bumetanide for all patients for a long period of time; LPS was inserted after the 1st surgery in 2 patients because of persistent elevated pressure (43, 52-cm H2O) who both reported recurrence of leak and need for a second repair after then. Yet, we reported no recurrence in any of the 17 cases after 8.2 months of follow-up. Unlike Chaaban et al. who treated pressures of 15-cm H2O with LDs plus acetazolamide and pressures of 35-cm H2O with VP shunts, Martinez-Capoccioni et al. had only one recurrence out of 25 spontaneous leaks after using acetazolamide and LDs. Campbell et al. reported 28% recurrence despite repair and treatment with acetazolamide. Sloiman et al. inserted LPS in all of his 18 patients and reported no recurrence [12–15]. Previous reports found that use of LDs in endoscopic CSF leak repair was associated with increased morbidity with no reduced recurrence rates [16, 17]. Nevertheless, the length of follow-up should be extended, as failures are suspected over time especially with continuously pulsatile forces of the elevated pressure in those patients especially if treatment is interrupted for any reason.

Five leaks recurred at the initial defect site; 7 evolved at a different site either on the ipsilateral ($n = 5$) or contralateral ($n = 2$) side. Two of the three patients with primary unidentified leak were detected at the cribriform plate and supraorbital recess in the repeat surgery, while the third patient remained unidentified even with the use of intrathecal fluorescein (possibly due to low CSF pressure from chronic leak) necessitating exposure and repair of the whole skull base. That is why a combination of CT, MRI, intrathecal fluorescein, and sometimes with Valsalva and Trendelenburg position is highly recommended. Woodworth et al. had three leaks failed at the primary site, and three additional leaks occurred at a new distant site. Interestingly, three of these patients had documented VPS malfunction further suggesting that elevated ICP may have directly contributed to the failures [9, 17].

In accordance with others [18, 19], failure to localize skull base defect contributed to patients requiring revision surgery in 17.6% within 1–2 months postoperatively. Although cribriform plate defects had higher incidence in the 2ry group ($n = 29.4\%$), they were associated with lower recurrence compared to LR of sphenoid (66.6% vs 20%) raising concern whether there is a need to change

Table 3 Criterion values and coordinates of the receiver operating characteristic (ROC) curve

Variable	Optimal criteriona	Sensitivity	Specificity	+PV	Area under the ROC curve (AUC)	Standard error	95% confidence interval	Significance level P
CSF pressure	> 39	29.41	95.00	83.3	0.607	0.0985	0.433 to 0.763	0.2760
BMI	> 29.07	100.00	45.00	60.7	0.710	0.0865	0.538 to 0.847	0.0150
Number of deliveries	> 1	92.31	72.22	70.6	0.803	0.0774	0.622 to 0.924	0.0001
Size of defect	> 1	76.47	80.00	76.5	0.765	0.0782	0.597 to 0.888	0.0007

material or technique of repair in this specific location or not. Lindstrom et al. noted that lateral sphenoid defects are difficult to visualize and had a higher rate of recurrence in their series [20]. Although statistically insignificant, we noticed that postoperative complications (meningitis (P-value = 0.584), COVID-19 (P value > 0.999), and pneumocephalus (P-value = 0.459) (Fig. 5) were linked to early recurrence.

Size of the defect correlated significantly to recurrence (P-value=0.001), whereas material of repair did not impact the outcome [9, 21], and hence, repair technique was standardized. The largest single-institution series did not note differences in recurrence rates based on reconstructive method using multilayer closure of free mucosal or overlay nasoseptal flap [12], however, Burns et al. discussed altering the method of closure depending on the size of the defect in the CP and FE [22]. Castelnuovo concluded some points that may improve the success of CSF repair, leak margins must be prepared accurately and cover at least 5 mm, and, for superior and lateral sphenoid sinus leaks, fat is better than other grafts [23].

Conclusion

Direct endoscopic visualization and repair of skull base defects achieve a high success rate, but failure is still a possibility especially in spontaneous etiology of leaks. Factors predictive of failure of the primary repair were multiparity, high BMI, symptoms and signs of increased ICP (blurred vision, unsteadiness, or MRI finding of empty sella+/− meningocele), failure to localize the defect, size of defect, and sphenoid lateral recess. Reconstructive material did not significantly predict a better outcome.

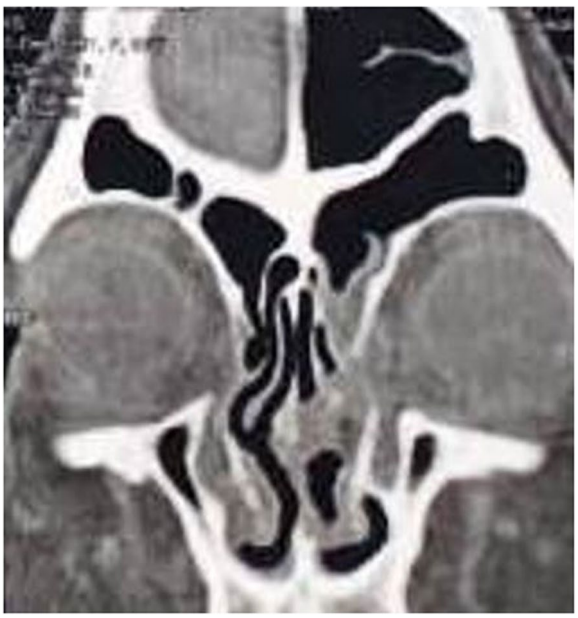

Fig. 5 Patient with left lateral lamella complicated by extensive pneumocephalus

Acknowledgements
Not applicable.

Authors' contributions
TAM, original conception, study design, data collection, interpretation and analysis, final approval, and agreement to be accountable for all aspects of the work; EHS, AHE, and WM, manuscript drafting and revision, study design and data interpretation, final approval, and agreement to be accountable for all aspects of the work; and YWK, original conception, study design, surgical treatment, final approval, manuscript drafting and revision, and agreement to be accountable for all aspects of the work.

Funding
The authors did not receive support from any organization for the submitted work.

Availability of data and materials
The datasets used and/or analyzed during the current study are saved with the primary investigator to protect confidentiality of participants and available on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Mansoura university institutional review board (IRB) (code no: MS.22.02.1891). An informed written consent to participate in the study was provided by all participants (or their parent or legal guardian in the case of children under 16).

Consent for publication
Informed written consent was obtained from all participants included in the study.

Competing interests
Dr Yasser W. Khafagy is a co-author of this study and an Editorial Board member of the journal. He has not handled this manuscript. The rest of the authors have no conflict of interest to declare.

Received: 5 July 2023 Accepted: 14 July 2023
Published online: 28 August 2023

References

1. Schlosser RJ, Woodworth BA, Wilensky EM, Grady MS, Bolger WE (2006) Spontaneous cerebrospinal fluid leaks: a variant of benign intracranial hypertension. Ann Otol Rhinol Laryngol 115(7):495–500
2. Chaaban MR, Illing E, Riley KO, Woodworth BA (2013) Acetazolamide for high intracranial pressure cerebrospinal fluid leaks. Intern Forum Allergy Rhinol 3(9):718–721
3. Schlosser RJ, Wilensky EM, Grady MS, Palmer JN, Kennedy DW, Bolger WE (2004) Cerebrospinal fluid pressure monitoring after repair of cerebrospinal fluid leaks. Otolaryngol Neck Surg 130(4):443–448
4. Schlosser RJ, Wilensky EM, Grady MS, Bolger WE (2003) Elevated intracranial pressures in spontaneous cerebrospinal fluid leaks. Am J Rhinol 17(4):191–195
5. Mirza S, Thaper A, McClelland L, Jones NS (2005) Sinonasal cerebrospinal fluid leaks: management of 97 patients over 10 years. Laryngoscope 115(10):1774–1777
6. Pérez MA, Bialer OY, Bruce BB, Newman NJ, Biousse V (2013) Primary spontaneous cerebrospinal fluid leaks and idiopathic intracranial hypertension. J Neuro-ophthalmology Off J North Am Neuro-Ophthalmol Soc 33(4):330

7. Konuthula N, Khan MN, Del Signore A, Govindaraj S, Shrivastava R, Iloreta AM (2017) A systematic review of secondary cerebrospinal fluid leaks. Am J Rhinol Allergy 31(6):e48–e56
8. Dandy WE (1937) Intracranial pressure without brain tumor: diagnosis and treatment. Ann Surg 106(4):492
9. Khafagy YW, Abd Elfattah AM, Moneir W, Salem EH (2018) Leukocyte-and platelet-rich fibrin: a new graft material in endoscopic repair of spontaneous CSF leaks. Eur Arch Oto-Rhino-Laryngol 275:2245–2252
10. Woodworth BA, Prince A, Chiu AG et al (2008) Spontaneous CSF leaks: a paradigm for definitive repair and management of intracranial hypertension. Otolaryngol Neck Surg 138(6):715–720
11. Teachey W, Grayson J, Cho D, Riley KO, Woodworth BA (2017) Intervention for elevated intracranial pressure improves success rate after repair of spontaneous cerebrospinal fluid leaks. Laryngoscope 127(9):2011–2016
12. Chaaban MR, Illing E, Riley KO, Woodworth BA (2014) Spontaneous cerebrospinal fluid leak repair: a five-year prospective evaluation. Laryngoscope 124(1):70–75
13. Martínez-Capoccioni G, Serramito-García R, Huertas-Pardo B, García-Allut A, Martín-Martín C (2015) Spontaneous cerebrospinal fluid leaks in the anterior skull base: a surgical challenge. J Laryngol Otol 129(4):358–364
14. Campbell RG, Farquhar D, Zhao N, Chiu AG, Adappa ND, Palmer JN (2016) Cerebrospinal fluid rhinorrhea secondary to idiopathic intracranial hypertension: long-term outcomes of endoscopic repairs. Am J Rhinol Allergy 30(4):294–300
15. Soliman AY, Ebeid K, Elfadle AA (2021) Recurrent spontaneous CSF rhinorrhea: combined endo-nasal endoscopic repair with lumbo-peritoneal shunt insertion. Egypt J Neurol Psychiatry Neurosurg 57:1–9
16. D'Anza B, Tien D, Stokken JK, Recinos PF, Woodard TR, Sindwani R (2016) Role of lumbar drains in contemporary endonasal skull base surgery: meta-analysis and systematic review. Am J Rhinol Allergy 30(6):430–435
17. Adams AS, Russell PT, Duncavage JA, Chandra RK, Turner JH (2016) Outcomes of endoscopic repair of cerebrospinal fluid rhinorrhea without lumbar drains. Am J Rhinol Allergy 30(6):424–429
18. Seth R, Rajasekaran K III, Luong A, Benninger MS, Batra PS (2010) Spontaneous CSF leaks: factors predictive of additional interventions. Laryngoscope 120(11):2141–2146
19. Wise SK, Harvey RJ, Neal JG, Patel SJ, Frankel BM, Schlosser RJ (2009) Factors contributing to failure in endoscopic skull base defect repair. Am J Rhinol Allergy 23(2):185–191
20. Lindstrom DR, Toohill RJ, Loehrl TA, Smith TL (2004) Management of cerebrospinal fluid rhinorrhea: the Medical College of Wisconsin experience. Laryngoscope 114(6):969–974
21. Elmorsy SM, Khafagy YW (2014) Endoscopic management of spontaneous CSF rhinorrhea with septal graft and middle turbinate rotational flap technique: a review of 31 cases. Ear Nose Throat J 93(6):E14-9
22. Burns JA, Dodson EE, Gross CW (1996) Transnasal endoscopic repair of cranionasal fistulae: a refined technique with long-term follow-up. Laryngoscope 106(9):1080–1083
23. Castelnuovo P, Mauri S, Locatelli D, Emanuelli E, Delù G, Di Giulio G (2001) Endoscopic repair of cerebrospinal fluid rhinorrhea: learning from our failures. Am J Rhinol 15(5):333–342

Publisher's Note