Endoscopic treatment of cerebrospinal fluid leaks with the use of lower turbinate grafts: a retrospective review of 125 cases*

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INTRODUCTION
Cerebrospinal fluid (CSF) leakage occurs when there is a communication between the subarachnoid space and the upper aerodigestive tract. CSF leaks may develop spontaneously, following traumatic injury, result from skull base tumours, or from surgery of the nose or paranasal sinuses (¹). The defect manifests itself with rhinorrhea as the main symptom. Even when no fistula is present, closure of the leak is necessary to prevent serious later complications (e.g., ascending bacterial meningitis, cerebral abscess, pneumocephalus) (²). Treatment of anterior skull base fistulae may be conservative or surgical. Conservative treatment entails bed rest and avoidance of physical exertion, prophylactic antibiotic therapy, and lumbar drain placement. This resolves the defect only in 50% of the cases, (³) however, it does not exclude the risk of ascending meningitis (²). Surgical repair of dural defects by craniotomy, as first described by Dandy in 1926, has a success rate of 60-80% (⁴); it affords the advantages of direct visualization of the dural defect and allows the repair of any type of fistula also with the use of a pedicled flap. The disadvantages are the need for a wide coronal incision, the risk of permanent anosmia due to injury of the olfactory bulb and the cribriform plate, intracranial bleeding and edema, and encephalomalacia after retraction of the frontal lobe (⁵,⁶). Extracranial surgery initially entailed accessing the skull base through nasoorbital incision (⁷).

Advances in endoscopic transnasal approaches to the skull base have revolutionized the treatment of CSF fistulae (⁸), allowing greater magnification and illumination and better exposure of defects, with success rates of over 90% at first
attempt (5,6,9-11). Together, these have made endoscopic surgery the method of choice in the repair of anterior skull base CSF leaks (12), though with limitations related to the site (posterior wall of the frontal sinus) and the size of the defect (5,13,14). Despite broad-based consensus on the validity of endoscopic surgery, considerable debate surrounds repair techniques (underlay, overlay, combined), graft material (autologous, heterologous), graft fixators (biological glue or nasal packing), and placement of a lumbar drain (15).

This study reports the results obtained with endoscopic repair of dural defects of the anterior skull base with the use of a lower turbinate mucoperiostal graft in a large patient series. A description is given of the technical details, the success rates, and the factors potentially responsible for repair failure.

MATERIALS AND METHODS

Patients’ diagnosis

Between January 1997 and January 2007, endoscopic endonasal repair of 125 cases of anterior skull base CSF leaks was performed at the Instituto Felippu de Otorrinolaringologia, Sao Paolo, Brazil, and the Department of Otolaryngology of the University Hospital “Ospedali Riuniti”, Foggia, Italy.

At history taking, details on present symptoms, comorbidities, past cranial trauma and craniofacial surgery were recorded. Rigid or flexible optic fiber rhinoscopy was performed with the patient’s head tilted downward and during the Valsalva maneuver to increase intracranial pressure and thus reveal fistula activity. Endoscopy was also useful for detecting associated sinonasal pathologies potentially responsible for causing the dural defect (e.g., previously treated nasal polyposis, neoplasms, etc.).

Treatment

CSF leakage was confirmed at β-2 transferrin testing and identified by means of high resolution computed tomography (HRCT), in some cases integrated with magnetic resonance imaging (MRI) according to the diagnostic algorithm of Zapalac (16). In occasional cases of doubtful fistula location, intrathecal fluorescein was used to identify the defect. In those cases of iatrogenic fistula arising during sinonasal surgery, no diagnostic procedure was performed and the defect was repaired intraoperatively. MRI studies were carried out when opacities on CT scans of the paranasal sinus aroused suspicion of meningocele or meningoencephalocele. In cases of spontaneous fistulae, MRI was performed to detect indirect signs of elevated intracranial pressure (ICP) such as hydrocephalus, transepidual edema and dilated temporal horns or the presence of empty or partially empty sella turcica (empty sella syndrome). Fistula size was calculated either by means of digital processing of the CT scan or intraoperatively on fistula exposure measured with a small sterile metric tape placed via endoscopy next to the dural defect using Blakesley pincers. At both study centers, the leak was closed with a mucoperiostal graft harvested from the lower turbinate by means of turbinoplasty and sized proportionally to the dural defect. Turbinoplasty was performed by making an incision on the head of the inferior turbinate, separating the submucoperiosteal tissue, and then removing the mental portion of the turbinate (bone and mucosal tissues); the mucosa of the nasal side was then flipped over to cover the exposed area. The graft was fashioned by accurate dissection of the mucosa with peristium from the turbinate bone of the removed portion. Wide exposure of the dura mater surrounding the defect was created to enable better graft take. Using an overlay technique, the peristomal side of the graft was placed in contact with the meninges. Fibrin glue was applied to stabilize the site, which was then covered with Surgicell. Accurate hemostasis under endoscopic control obviated the need for nasal packing.

Patient recovery

During the early post-operative period, patients were prescribed bed rest with the head raised to 30°, a cool liquid diet for 5 days, and a 6-day course of antibiotic therapy with a third generation cephalosporin. No lumbar drain was placed after the first operation. Patients were advised to rinse the nasal cavity with sterile, lukewarm saline solution and to avoid physical exertion or maneuvers that could increase intracranial pressure (nose blowing or sneezing with mouth closed) for at least one month following the operation.

Follow-up

The minimum duration of the postoperative follow-up period was 2 years (range, 24-132 months; mean follow-up, 96.6), with weekly endoscopic control visits during the first month, monthly over the next 3 months, and then yearly up to 5 years postoperative to check for possible leak recurrence.

RESULTS

Pre-treatment results

This series comprised 125 patients (68 males, 57 females; mean age, 57.2 years; range, 25-85) who underwent endoscopic endonasal repair of CSF leaks. History taking disclosed unilateral watery rhinorrhea in 102 (81.6%) patients, headache in 79 (63.2%), recurrent meningitis in 45 (36%), and hyposmia in 22 (17.6%). The duration of rhinorrhea was less than 7 days in 32 patients, 7-30 days in 41, and more than 30 days in 29. Comorbidities included diabetes mellitus in 5 (4%) patients, high blood pressure in 15 (12%), heart disease in 6 (4%), and hypercholesterolemia in 2 (1.6%). β-2 transferrin analysis confirmed CSF leakage in all cases of active fistula (81.6%). The etiology of the fistula was accidental trauma in 41 (32.8%) patients, iatrogenic trauma in 29 (23.3%), spontaneous in 43 (34.4%), and skull base tumour in 12 (9.6%). Fistulae of traumatic origin resulted from road accident in 20 (16%) patients, personal assault in 13 (10.4%), domestic accident in 4 (3.2%), explosion in 3 (2.4%), and gunshot wound in 1 (0.8%). Iatrogenic fistulae arose during a sinonasal procedure in 18...
(14.4%) patients and pituitary surgery in 11 (8.8%). These 29 cases of iatrogenic fistulae were recorded out of a total of 6562 operations in advanced endoscopy performed at the two study centers and account for 0.27% of the total complications rate. In 20 out of these 29 patients, the fistula was detected during the operation and promptly repaired; in the remaining 9 patients, the defect was detected in 1 patient during subsequent treatment at the same institution and in 8 patients during treatment at other institutions. Spontaneous fistulae were more prevalent among women (29 cases; 67.4%) than men. This patient subgroup presented with a high rate of comorbidities: diabetes mellitus in 5 (4%) patients, high blood pressure in 10 (8%), hypercholesterolemia in 2 (1%), and heart disease in 3 (2.4%).

The site of the fistula was identified at ambulatory endoscopy in combination with the Valsava maneuver in 42 (33.6%) patients, at HRCT in 41 (32.8%), at MRI cisternography in 6 (4.8%), intraoperatively with accurate dissection of the nasal floor of the anterior skull base in 32 (25.6%), including the 20 cases of iatrogenic fistula that occurred during surgery, and intraoperatively with intrathecal fluorescein in 4 (3.2%). The site most often affected was the sphenoid sinus (43 patients; 34.4%), followed by the cribriform plate (42; 33.6%), the anterior ethmoid roof (21; 16.8%), the posterior ethmoid roof (17; 13.6%) and the posterior wall of the frontal sinus (2; 1.6%) (Figures 1 and 2). The fistulae varied in size from 0.1 to 2.8 cm (mean 1.1 cm): 88 (70.4%) patients presented with a fistula less than 2 cm and 37 (29.6%) with a defect more than 2 cm (Table 1).

MRI was performed in 77 (61.6%) patients: 12 with skull base tumour, 43 with spontaneous fistula, 22 with fistula from accidental trauma. Meningoencephalocele was detected in 24 (19.2%) patients. Indirect signs of elevated ICP were found in 38 (30.4%) patients, 31 of which presented with spontaneous fistula, 5 with fistula of traumatic origin, and 2 with fistula associated with skull base tumour (Figure 3). Among the 31 (72%) patients with spontaneous fistula and signs of elevated

<p>| Table 1. Characteristics of cerebrospinal fluid fistulae. |</p>
<table>
<thead>
<tr>
<th>No./total</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>43/125</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>29/125</td>
</tr>
<tr>
<td>Traumatic</td>
<td>41/125</td>
</tr>
<tr>
<td>Associated with skull base tumors</td>
<td>12/125</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
</tr>
<tr>
<td>Sphenoid</td>
<td>43/125</td>
</tr>
<tr>
<td>Cribriform plate</td>
<td>42/125</td>
</tr>
<tr>
<td>Anterior ethmoid roof</td>
<td>21/125</td>
</tr>
<tr>
<td>Posterior ethmoid roof</td>
<td>17/125</td>
</tr>
<tr>
<td>Posterior wall of frontal sinus</td>
<td>2/125</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 cm</td>
<td>88/125</td>
</tr>
<tr>
<td>≥ 2 cm</td>
<td>37/125</td>
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Figure 1. Endoscopic view of CSF fistula of the posterior wall of the frontal sinus (arrow) during a Lothrop procedure. Ample exposure of the dura mater facilitates mucoperiostal graft take.

Figure 2. Endoscopic view of the posterior wall of the frontal sinus (arrow) at ten days postoperative.

Figure 3. Patients with signs of intracranial hypertension. (hydrocephalus, periependymal edema, dilated temporal horns).
Endoscopic treatment of CSF leaks

ICP, 11 (35.4%) presented with empty or partially empty sella turcica and 2 (6.4%) with hydrocephalus.

**Post-treatment results**

CSF leak repair was successful at first attempt in 118/125 (94.4%) patients. The 7 patients (2 men, 5 women) with postoperative leak recurrence initially presented with spontaneous fistula and signs of elevated ICP; 5 of them had a body-mass index (weight in kg divided by height in meters squared [BMI]) over 30 and 3 suffered from diabetes mellitus. A BMI over 30 was noted in 3 other patients in the group with spontaneous fistulae and in only 2 patients in the other groups. The site of recurrence, as detected at endoscopy, HRCT or MRI, was the ethmoid roof in 5 cases and the lateral wall of the sphenoid sinus in 2 (the same location as the pre-operative fistula). The fistulae were less than 2 cm (mean 1.1 cm) and the sella turcica was empty or partially empty in all cases. Postoperative CSF leakage occurred several days after the operation in 3 patients and was resolved with placement of a lumbar drain for 10 days. In the 4 patients with delayed postoperative CSF leakage (2-10 months), the leak was repaired by endonasal endoscopy and an underlay technique using lyophilized dura covered with a new mucoperiostal graft harvested from the other lower turbinate (Table 2). At follow-up examination 3 months later, the defect had completely resolved.

**DISCUSSION**

Key to the success of surgical CSF leak repair is correct diagnosis of the presence, site and size of a fistula. The universally accepted test for determining the presence of a fistula is β-2 transferrin analysis owing to its high sensitivity and specificity (16,17), given the possibility of a false positive finding of unilateral CSF rhinorrhea at history taking, which may be confirmed in some cases (18). In recent years the use of β-trace protein has gained wide acceptance as an immunological marker for detecting CSF leakage. It is faster and less expensive than the β-2 transferrin test, but both methods have high diagnostic accuracy (19,20). Doubtful location of a fistula is considered by many investigators as one of the main causes of repair failure (21), making it all the more important to determine the exact site of the defect before undertaking surgical intervention. In this series, we applied Zapalac’s diagnostic algorithm, which entails HRCT, while an MRI study was reserved for cases where HRCT failed to identify the defect, or in the presence of bony erosions, or of masses of uncertain significance (16). Departing from this algorithm and that used by other investigators (17), we rarely used intrathecal fluorescein in doubtful cases. Although a valuable diagnostic tool for detecting skull base defects, intrathecal fluorescein injection is not devoid of potential risks and it has been variously reported to cause extremity numbness, tingling, absence seizure, opisthotonus, and death (generally at high doses) (6,22,23). So in cases where the defect cannot be detected by ambulatory endoscopy or HRCT or MRI cisternography, we advocate searching for dehiscence by accurate dissection of the ethmoid or the sphenoid roof. Anteroposterior ethmoidectomy with exposure of the nasal floor of the anterior cranial fossa, in combination with sphenoid sinusotomy and the patient placed in Trendelenburg’s position (to raise CSF pressure), enabled us to identify the fistulae in 32 (25.6%) cases not revealed at imaging (including the 20 cases of iatrogenic fistula) and to restrict its use to only 4 (3.2%) patients. In cases where intrathecal fluorescein is indispensable, a viable alternative to intrathecal injection is topical endonasal application of fluorescein to reveal microdefects that would be otherwise difficult to visualize with simple endoscopy or HRCT scanning (21).

Endoscopic endonasal surgery is currently considered the treatment of choice for the closure of CSF leaks (22), given that the success rates reported for the past decade (over 90% at first attempt on average) (24) are clearly higher than those obtained with conservative treatment or craniotomy or extracranial approaches. The complications associated with this technique are rare. Senior et al. reported a rate of 2.5% in a sample of 650 cases of endoscopic repair for CSF leakage and encephalocele obtained from a questionnaire survey of 72 otorhinolaryngolo-
ists of the American Rhinologic Society who regularly performed this type of procedure. Complications after CSF leak repair included: seizure, meningitis, and only one reported case each of cavernous sinus thrombosis, temporary visual problems, sinusitis, intracranial hypertension and death (25). In a meta-analysis of studies published in English between 1990 and 1999, Hegazy et al reported an incidence of less than 1% of major complications such as meningitis, subdural hematoma and intracranial abscesses for each complication (26).

In our series, no major complications occurred. The debate surrounding the choice of technique remains open, particularly about the type of graft material for fistula repair: autologous grafts harvested from the nasal septum, the middle or lower turbinate (with bony, mucoperichondrial or mucoperiostal component), abdominal fat, temporal fascia and fascia lata; homologous grafts (cadaveric pericardium or lyophilized dura mater); allografts (hydroxyapatite). The technique of graft positioning may be by underlay (between the dura mater and the skull base) or by overlay (apposition on the nasal side of the skull base) or by obliteration of the involved paranasal sinus (2,5,6,10,11,13,14,21,24,28).

Our technique entails overlaying a mucoperiostal lower turbinate graft to close fistulae from 0.2 to 2.8 cm. In this series of patients treated at two different centers, the success rate with this technique was 94.4%, higher than that reported in other studies (2,10,28-30). Of note is that at the two centers the surgical technique was standardized with the use of procedures that helped to ensure the success rates could be improved. A key element in this direction was graft choice and preparation. Specifically, the lower turbinate is an ideal donor site for mucoperiostal grafts in that it is sufficiently thick and provides a wide surface. The use of conservative turbinoplasty allowed for harvesting an adequately large portion of mucoperiostal or nasal meatus tissue, including a minimum amount of bone, without altering lower turbinate function, thus reducing the risk of creating an abnormally large empty nose, as often occurs with turbinectomy. The harvested material is then prepared by accurate dissection of the periostium from the underlying bone. Periostal integrity, which constitutes the part placed over the dura mater, is essential for graft take. The mucoperiostal graft is then fashioned to a size at least 5 mm greater than the defect. On the mucosal side a thin layer of Surgicell is applied so that it can be distinguished from the periostal side when introduced into the nose.

Highly important is adequate preparation of the repair site: the area around the fistula needs to be accurately identified and cleaned, removing the mucosal lining to expose the dura mater around the defect, and flattening any bony spurs (Figure 1). The graft is then positioned under endoscopic control with the mucoperiostal side in contact with the exposed dura mater. Fibrin glue is then injected into the interstitial space between this structure and the area of dehiscence, as application of the glue before positioning the graft could create folds and imperfections. Finally, the graft is fixed with Surgicell strips to protect it during attachment. No patients in this series required nasal packing at completion of the operation.

In our experience, and as reported elsewhere, fibrin glue was found to improve graft attachment (10,15,28). As demonstrated on rats (31), this material is devoid of risk as it causes no brain damage if it accidentally spreads through the fistula. The overlay technique is preferable to the underlay technique because of fewer risks related to graft positioning. In the underlay technique, separation of the dura mater from the overlying bone and subsequent placement of the graft increases the risk of injury to vascular or nervous structures (5). In this series, only in 4 cases of postoperative CSF leak recurrence was it necessary to use a combined approach (lyophilized dura placed with an underlay technique and the mucoperiostal graft positioned using the overlay technique) to obtain a watertight, more resistant closure.

As demonstrated by Zweig et al. (5), we also found that the defect size (here, 0.2-2.8 cm) did not appear to influence repair outcome. Moreover, postoperative leaks also occurred in fistulae measuring less than 2 cm. These observations contrast with theories that contraindicate the use of free grafts to repair defects over 3 mm, because of the potential risk of meningoceles or meningoencephaloceles (24,29), or sustain that extracranial approaches are dictated for closing fistulae more than 1.5 cm (14). Among our patients, no cases of meningoceles or meningoencephaloceles were observed at 1 year follow-up. In line with our results are those reported by Gjuric who used free lower turbinate mucoperiostal grafts to close defects ≤ 10 x 10 mm (30). In brief, we believe that only defects over 3 cm require composite grafts or combined underlay-overlay approaches (28); otherwise, free grafts accurately positioned with an overlay technique appear adequate for successful fistula closure. Also, the anatomical site of the defect did not influence repair outcome. In our series, even fistulas of the posterior wall of the frontal sinus, generally considered a limitation to endoscopic approach, were successfully repaired (Figure 2).

Analysis of repair failure in this series showed that all occurred in patients with a spontaneous fistula. According to current theory, the defect is secondary to elevated ICP and acts as a pressure valve that in patients with persistently elevated ICP releases the pressure through ruptures in the thinnest areas of the skull base (cribriform plate or walls of the highly pneumatized paranasal sinuses). This notion is supported by evidence from studies by Schlosser (32,33) that found symptoms suggestive of elevated ICP (pulsating tinnitus and headache in successfully closed fistulae), indicating that the intervention might have restored the preoperative hypertensive state. Measurement of ICP by means of lumbar drainage confirmed elevated values in nearly all patients (32,33).

In our series, the potential role played by ICP in the pathogen-
esis of spontaneous fistula formation was confirmed by the considerable number of cases of empty or partially empty sella turcica at preoperative assessment (11 patients; 25.5%) and in all cases of postoperative leak recurrence. Elevated ICP is known to provoke herniation of the meninges and CSF through the sella diaphragm, which exerts compression on the hypophysis, with radiographic evidence of a completely or partially empty sella. Since this condition was often encountered in patients with spontaneous fistula, it may be considered a potential pathogenetic factor, together with other skull base malformations and increased pneumatization of the sphenoid sinus, which renders the wall thinner and more susceptible to injury. In this connection, the prevalence of spontaneous fistulae among the female patients was most likely due to the thinner bone thickness of the sinus walls in these subjects. Directly correlated with ICP was the repair failure rate among the obese patient in our series. Several studies have shown that obesity is a determinant factor for repair failures; ICP in these patients was correlated with increased intra-abdominal pressure and pleural pressure, with a cardiac filling defect that impedes venous return from encephalic circulation. Other theories sustain that obesity is not the cause, but rather the effect of diminished absorption of CSF that can lead to compression of the hypophysis and result in endocrine-metabolic imbalance.

In agreement with various studies is our observation that spontaneous fistula is a negative prognostic factor for successful repair. This assumption is warranted when we realize that repair surgery treats the symptoms, but not the cause in so far as elevated ICP, which persists after fistula closure, inhibits graft take, creating the conditions for the formation of a new fistula. This makes it advisable to combine repair of the defect with treatment of its cause to control for the factors underlying elevated ICP.

Optimal results were achieved in cases of recurrence relatively soon after the operation by placing a lumbar drain that regulated ICP and inhibited abnormal stress on the graft. Routine postoperative lumbar drain placement is controversial because of possible side effects (nausea, vomiting, headache, pneumoencephalus, meningitis and brain tissue herniation), given that the results are not always better than those in patients who do not receive lumbar drainage. We believe, however, that the use of lumbar drainage is warranted in cases of spontaneous fistula in which radiographic evidence suggests increased ICP. In those patients with increased ICP (24.8% in our series), drain placement might have reduced the number of repair failures. In cases of spontaneous fistulae with cranial scans negative for ICP, administration of acetazolamide may help to reduce ICP.

Other simple care measures that reduce ICP include bed rest, use of laxatives, recommendation not to blow the nose or sneeze with the mouth closed, and to avoid physical exertion for at least 1 month following the operation. Equally important is cleaning the nasal cavity with frequent nasal rinses with sterile, lukewarm saline solution starting postoperative day 2 (avoiding the use of pressurized sprays owing to possible trauma), as well as ambulatorial medication for aspirating secretions and removal of crust and support material (Surgicell in our series). All procedures should be carried out with extreme caution to avoid damaging graft attachment.

CONCLUSION

Repair of anterior skull base CSF fistulae with the use of a mucoperiosteal lower turbinate graft, when correctly done with careful attention to the technique of exposure of the dura mater and accurate apposition of the graft, kept in place with fixators (fibrin glue) and supports (Surgicell, Spongostan), permits the restoration of dural continuity in a majority of cases, also in the presence of defects more than 2 cm, for which repair with composite grafts is usually indicated. These results may be further improved by controlling for factors that contribute to elevated ICP, which undermines the success of spontaneous fistula repair. When ICP is suspected, its precise causes should be sought. Prompt treatment in such cases includes lumbar drain placement to reduce pressure on the graft and thus facilitate graft take.

REFERENCES