Introduction

Cerebrospinal fluid (CSF) may pathologically communicate with the outside world. This may be caused by a diverse set of etiologies. Diagnosis and treatment can be challenging and continues to evolve. This manuscript will explore the pathophysiology and management of CSF fistulae.

History

CSF rhinorrhea has been described as far back as the time of Galen (16). In the Middle Ages an association with head trauma (2). The topic was first reviewed by Miller in 1826 (2). Spontaneous CSF otorrhea was first described in 1897 by a French physician in a 10-year-old girl who had had intermittent otorrhea for eighteen months and a fistulous opening in roof of the inner third of her ear canal. With cautery the otorrhea ceased (7). Dandy first described an intracranial repair of a CSF leak in 1926, and Dohlman in 1948 was the first to describe the extracranial repair, which he did via a naso-orbital incision for an anterior cranial fossa CSF leak. Hirsch and later Vrabec described trans-nasal approaches, and Wigand in 1981 was the first to describe the use of endoscopes in the repair of small leaks incurred during ethmoidectomy (11). The last twenty years has seen a refinement in the techniques and materials used for endoscopic repair of CSF leaks and encephaloceles.

Basic Science

Cerebrospinal fluid is manufactured mostly in the choroid plexus in the lateral ventricles. It then traverses the third and fourth ventricles where it egresses into the subarachnoid space via the foramina of Luschka and Magendie. It circulates throughout the meninges between the arachnoid and the pia and provides a layer of protection for the neural tissue. It is reabsorbed by the venous system via arachnoid villi which project into the venous sinuses (3).

The composition of CSF is similar to that of serum with some minor differences. More importantly, as an ultrafiltrate of serum, abnormalities of serum values (hyperglycemia, for example) will be reflected in the CSF, given enough time for equilibrium to be reached. Adults average 140 mL of CSF volume, and the pressure of CSF under normal conditions can range between 50 and 180 mmH2O. A new body regenerates its CSF volume three times per day.

Beta-2-tranferrin is a protein which is only found in CSF, perilymph, and vitreous humor (5). It deserves special mention as an important marker when one is trying to determine the etiology of nasal discharge, as it generally indicates a CSF leak.
Classification

As the study of CSF leaks has progressed the literature has not had a consensus regarding the terminology used to describe them. A recent editorial by Har-El summarized here may resolve some of the confusion.

CSF leaks may be traumatic or non-traumatic. Traumatic leaks may be surgical or non-surgical, and surgical leaks may be planned (e.g. failed reconstruction) or unplanned, while non-surgical leaks may be penetrating or non-penetrating. All of the above may be subclassified as either immediate or delayed.

Non-traumatic leaks may be subdivided as high pressure or normal pressure leaks. High pressure leaks may be due to tumors, hydrocephalus, or benign intracranial hypertension. Normal pressure leaks may be due to a variety of reasons, including congenital defects, tumors, arachnoid granulations, infection, empty sella, and idiopathic causes (9).

An older scheme which persists in the literature includes the one devised by O'Connell. He divided spontaneous CSF leaks into “primary spontaneous” leaks which were idiopathic in origin, and “secondary spontaneous” leaks in which a cause was identified. Ommaya preferred avoiding the use of the term “primary spontaneous” as a wastebasket classification for which a cause has not been discovered, and advocated avoidance of the use of “secondary spontaneous” as a logistically impossible phrase. Har-El notes that many of the “spontaneous” leaks are probably delayed-onset non-surgical traumatic leaks and avoids the term “spontaneous” altogether, reserving “idiopathic” for cases in which no cause can be identified. Nevertheless, the term “spontaneous” persists in the literature and in practice to refer to leaks which appear without a clear antecedent trauma.

Another important designation when evaluating a CSF leak is that of high-flow or low-flow. A high-flow leak can be actively seen. A low-flow leak cannot, but its presence is highly suspected clinically (for example, a post-op FESS patient with unexplained pneumocephalus). In general a low-flow leak is more difficult to diagnose but responds better to more conservative measures, whereas in a high-flow leak the converse is true.

Epidemiology

Approximately 80% of CSF fistulae with resultant rhinorrhea are caused by non-surgical trauma, 16% by surgical trauma, with only 3-4% having a non-traumatic cause (2). CSF fistulae have been found to occur in 3% of closed head injuries, 9% of penetrating head injuries, and 10% to 30% of basilar skull fractures (12). Traumatic fistulae are most common in males in the third to fifth decades. Eighty percent will present in the first 48 hours, and 95% will present by three months (16). Meningitis occurs in between 10% and 25% of head trauma cases with a CSF leak (6) has a mortality of approximately 10% (12). Series from the first half of the century indicate that two-thirds of post-traumatic CSF leaks will resolve spontaneously by one month (1). Post-traumatic leaks are 80% cranio-nasal and 20% cranio-aural, with the latter having a better chance of spontaneous closure (1).

As far as otologic issues related to CSF leaks, spontaneous CSF otorrhea is rare and usually presents in childhood with symptoms referable to labyrinthine malformations (such as a Mondini deformity) or meningitis (7). In one series the median age of presentation was four years, with 92% presenting with recurrent pneumococcal meningitis and 86% with an associated unilateral or bilateral sensorineural hearing loss (15). Most cases of CSF otorrhea follow trauma, and the second-most common cause is post-surgical. After trans-labyrinthine acoustic tumor surgery, a large series from the House Ear Clinic showed an incidence of CSF leaks of 6.8%, and found that it was unrelated to patient age, tumor size, or operative time. Meningitis occurred 2.9% of the time and was only related to larger tumors (14).

Diagnosis

Unless identified at time of surgery, diagnosing a cerebrospinal fluid fistula can be difficult. A high index of suspicion must be present in patients with unilateral rhinorrhea. Of note, rhinorrhea may be a sign of a fistula of aural origin via the eustachian tube. A thorough history may reveal an antecedent history of trauma or meningitis. Depending on the clinical picture the physician has a variety of different tests he or she may employ.

The simplest tests are easy to perform but not very accurate. The halo sign is present when nasal secretions on bed linens or dressings form a halo. This occurs when CSF, mixed with blood, spreads onto
an absorbent surface. The darker blood chromatographically forms a ring around a lightly-stained center, forming a halo (5). Mixture of blood with tears or saliva can give false-positives.

Another simple test involves collecting rhinorrhea on a handkerchief. Nasal secretions will dry and leave a stiff residue, whereas CSF will dry and leave the cloth soft.

The laboratory plays a key role in the diagnosis of CSF rhinorrhea. One of the more simple things for which to check is glucose. Normally nasal secretions are devoid of glucose whereas CSF has a glucose level related to the plasma glucose. The literature generally supports a glucose value of 30 mg/dL in rhinorrhea fluid as indicative of CSF. However, there are opportunities for false-positives and false-negatives. For example, a post-surgical patient may have a serous exudate which physiologically contains glucose. Conversely, a patient with an advanced meningitis may have a decrease in his or her CSF glucose (see Table 1).

The gold standard for laboratory diagnosis of CSF fistulae is beta-2-transferrin. This protein is found in only three bodily fluids – CSF, perilymph, and vitreous humor (5). Therefore, unless a patient has an open globe, ongoing production of clear nasal discharge that is positive for beta-2-transferrin is highly diagnostic for CSF. At our institution the lab requires 1 mL of nasal or oral secretions and an SST tube of blood (gold-topped tube). Results are reported in four days.

At times collection of rhinorrhea can be a problem. In a comatose patient one can turn the patient onto his or her side and try and collect fluid, or in an alert patient one can have the patient Valsalva to try and increase flow. Additionally one may collect fluid and elicit a physical exam finding when checking for the reservoir sign – in this the patient is supine for a length of time and then brought into an upright position with the neck flexed. A rush of clear fluid is a sign of a fistula. If these measures are unsuccessful one must turn to alternate means of diagnosis.

Radionuclide cisternography may be useful when the presence of a CSF leak is in question. In this technique radioactive tracers are injected intrathecally and then cotton pledgets are placed intranasally. Pledgets are placed high near the sphenoïd, in the middle meatus, and low near the eustachian tube orifice. The pledgets are collected and then compared to plasma by means of scintigraphy. Enough counts on the pledgets suggest a leak. The two most commonly used isotopes are technetium 99m-labeled albumin (half-life 6 hours) and indium 111-labeled DTPA (half-life 2.8 days) (12). This technique is very sensitive but not very specific as false-positives may occur. Similar techniques involving dyes are of historical interest but were abandoned due to poor efficacy and high rate of complications (16).

When a leak is actively flowing the radiological procedure of choice to localize the lesion is CT cisternography. In this technique non-ionic contrast is instilled intrathecally and the patient scanned via standard computed tomography. In addition to the bony detail afforded by CT, the addition of contrast allows the leakage of CSF to be seen and thus assists in the localization of the defect. Magnetic resonance imaging (MRI) may sometimes be a useful adjunctive study if mass lesions or encephaloceles are present (11).

Another intrathecal agent that can assist the surgeon is fluorescein. This bright green-yellow dye can be instilled intrathecally and then used to assist the surgeon locate the defect via direct visualization. Although its use has somewhat been curtailed due to neurological sequelae, Burns reports the use of 0.5 ml of 5% solution without complications. It can be given simultaneously with contrast material, and thus one can use CT cisternography and endoscopic examination in a complementary fashion (4).

Treatment

Treatment can be divided into surgical and non-surgical (medical) measures. In general surgical measures are used for leaks not responding to conservative measures, open wounds, wounds made and identified during surgery, and for lesions with other associated complications such as intracranial hemorrhage or tension pneumocephalus. Medical management can be used as initial management when there is a chance that the body will repair the defect itself and there is not significant risk associated with delaying repair (16).

Medical management consists of a number of measures that are designed to decrease the flow through the fistula site. These include elevation of the head of bed and avoidance of coughing, sneezing, or straining at stool. Anti-tussives and laxatives are given. Anti-hypertensives and analgesics are given as needed. The patient is confined to bedrest. CSF is removed via a lumbar drain. Different authors advocate different rates, such as 50 cc removed every 8 hours (5) or 10 cc every hour (11). Care must be used not to
remove excessive amounts of CSF, though, or risk an iatrogenic pneumocephalus. The use of prophylactic antibiotics is controversial and will be discussed below.

Surgical management is tailored to the individual, and for many situations there is more than one way to approach them. However, there are general considerations which apply. The otolaryngologist will most often be repairing skull-base defects through an extracranial approach, and discussions of intracranial repairs can be found elsewhere. Some of the controversies about the two approaches will be discussed below. For the otolaryngologist, extracranial repair is either done with the endoscope or with the operating microscope (11).

For sphenoid or ethmoid fistulae, exposure of the defect is key, with care in the sphenoid region to perform the minimum sphenoidotomies necessary for exposure in order to prevent graft extrusion. Next mucosa is removed from around the defect in order to give the graft a site to which it may adhere. Any cephaloceles are dealt with appropriately by reduction or excision. The next step is plugging of the defect, and different authors employ different techniques. Some options that one has include intracranial or extracranial graft placement, use of abdominal fat grafts, use of fascia or muscle from a variety of locations, grafts or flaps from the septum or the middle turbinate, choice of simple or composite grafts or flaps, and reinforcement with adjunctive materials such as fibrin glue, cyanoacrylic glue, or microfibrillar collagen. In general most authors employ some combination of the above, and then support the grafts/flaps with absorbable gelatin sponges and removable supports such as balloons or nasal tampons (1,4,6,8,11,12).

Frontal sinus defects are repaired in a similar fashion, with frontal sinus exposure via osteoplastic flap, repair of dural defect, fascial graft support, and frontal sinus obliteration with abdominal fat (6).

A patient who has facial fractures and a CSF leak may spontaneously close the fistula when the fractures are reduced. The decision to address the fistula at the time of fracture reduction must be individualized to the patient, but in an unstable patient in whom an extensive general anesthesia may be undesirable, the decision to delay the surgical treatment of a potential CSF fistula until after treatment of facial fractures is a defensible one, as the fracture reduction aids healing of dural tears (6,12).

Postoperative care includes many of the measures discussed before. Avoidance of sneezing and coughing, use of laxatives to avoid straining at stool, elevation of the head of bed, and bedrest are important to give the grafts time to heal. Other measures such as the use of a lumbar drain and antibiotics are controversial.

Controversies

One controversy regards the use of prophylactic antibiotics. If a CSF leak is diagnosed, should one treat empirically to avoid meningitis? Proponents argue that meningitis is bad enough to warrant the use of prophylactic antibiotics despite no data which show their efficacy. Opponents feel that they are ineffective and lead to colonization by more serious flora. One author who recently reviewed the literature concluded: “The use of prophylactic antibiotics is neither recommended or condemned by evidence of efficacy. However, their use is cautioned against by evidence of a subsequent change in nasopharyngeal flora to potentially more invasive organisms” (13).

Another controversy that arises is the benefits of intracranial repair versus extracranial repair. Advantages of an intracranial approach include direct visualization, the ability to repair adjacent cortex, and a better chance of repairing a leak caused by increased intracranial pressure. The disadvantages include increased morbidity, longer hospitalization, and higher incidence of post-operative anosmia. On the other hand, and extracranial repair has decreased morbidity and anosmia, as well as superior exposure of the posterior ethmoid, parasellar, and sphenoid regions. However, it is less suited for defects in the frontal sinuses with prominent lateral extension and is less successful in high-pressure leaks (16). Although the literature generally shows a higher successful rate of repair with extracranial approaches, in the end the choice of approach depends on the experience of the surgeon and the particular details of the case at hand (1,10,11).

Other treatment decisions exist in which clinicians do not have the benefit of scientific studies to guide them, and these decisions usually fall to the experience of the surgeon and the clinical scenario. Examples of these include the use of a lumbar drain post-operatively, the length of time to try conservative measures before proceeding with surgery, and the best materials and approaches with which to close defects.
Complications

Meningitis refers to the inflammation of the meninges, and this is a possible sequela of a CSF fistula and can occur post-operatively as well. Traumatically-acquired meningitis occurs in between 10% and 25% of cases (6) has a mortality of approximately 10% (12). The pathogen depends on the presentation and is summarized in Table 1. The patient will feel sick and may have a stiff neck, photophobia, headache, fever, mental status changes, and Kernig’s sign (pain upon extension of the knee when the thigh is flexed). Post-operatively this may be due to a microbial etiology or may be due to chemical irritation. Diagnosis is aided by lumbar puncture and appropriate therapy is begun. CSF findings in different forms of meningitis are summarized in Table 2. Other infectious complications such as frontal lobe abscess are possible as well (4).

Another serious complication of a CSF fistula is tension pneumocephalus. Occasionally this can be a patient’s presentation (10), but the surgeon needs to be aware that this can be a consequence of overaggressive lumbar drainage. The patient can undergo a progressive neurological deterioration, and immediate neurosurgical intervention is indicated. Plain film is the quickest way to make the diagnosis.

### Table 1. Types of meningitis and causation organisms

<table>
<thead>
<tr>
<th>Type</th>
<th>Organism(s)</th>
<th>Appearance</th>
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<tbody>
<tr>
<td>Spontaneous</td>
<td></td>
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<tr>
<td>Neonatal</td>
<td><em>Escherechia coli</em></td>
<td>Gram-negative rods</td>
</tr>
<tr>
<td>Pediatric</td>
<td><em>Haemophilus</em></td>
<td>Gram-negative rods</td>
</tr>
<tr>
<td></td>
<td><em>Meningococcus</em></td>
<td>Gram-negative cocci</td>
</tr>
<tr>
<td></td>
<td><em>Pneumococcus</em></td>
<td>Gram-positive cocci</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pneumococcus</em></td>
<td>Gram-positive cocci</td>
</tr>
<tr>
<td></td>
<td><em>Meningococcus</em></td>
<td>Gram-negative cocci</td>
</tr>
<tr>
<td>Posttraumatic*</td>
<td><em>Staphylococcus aureus</em></td>
<td>Gram-positive cocci</td>
</tr>
<tr>
<td></td>
<td><em>Pneumococcus</em></td>
<td>Gram-positive cocci</td>
</tr>
<tr>
<td>Postoperative*</td>
<td><em>Staphylococcus aureus</em></td>
<td>Gram-positive cocci</td>
</tr>
<tr>
<td></td>
<td><em>Pneumococcus</em></td>
<td>Gram-positive cocci</td>
</tr>
</tbody>
</table>

*With or without a cerebrospinal fluid leak.* (adapted from Constantino)

### Table 2. Cerebrospinal fluid evaluation for meningitis

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Aseptic (chemical)</th>
<th>Bacterial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Clear</td>
<td>Clear</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Gram stain</td>
<td>Negative</td>
<td>Negative</td>
<td>Bacteria present</td>
</tr>
<tr>
<td>Protein</td>
<td>&lt;40 mg/100 mL*</td>
<td>Normal to slightly elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Glucose</td>
<td>45–80 mg/100 mL</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>RBC</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>WBC</td>
<td>0–5 cells/mL</td>
<td>Normal to slightly elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Pressure (recumbent)</td>
<td>&lt;200 mm H₂O</td>
<td>Normal to slightly elevated</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

*RBC, red blood cells; WBC, white blood cells.*

*A traumatic lumbar puncture can introduce RBCs into the CSF. In this setting, for every 700 RBCs there is usually 1 WBC and the protein is elevated by 1 mg/100 mL. This should be taken into account when interpreting cerebrospinal fluid (CSF) analysis results. Further, polymorphonuclear leukocytes should be considered abnormal until proven otherwise as normal CSF only contains lymphocytes and monocytes.* (adapted from Constantino)

New Horizons

Endoscopic repair of CSF fistulae is continuing to be refined, and it is possible that this will become the standard of care. The optimum methods and materials used to repair fistulae will likely be elucidated in the future, as well as the possibility of new biomaterials which may provide improved success in closing CSF fistulae. Radiologic techniques have continued to improve and assist the head and neck surgeon, and surely there will be advances in the future to improve the diagnosis and localization of skull base defects.

Conclusion
Cerebrospinal fluid fistulae may arise from a variety of etiologies. Diagnosis is based upon history, physical, laboratory, and radiological factors. Treatment consists of non-surgical and surgical means. The otolaryngologist/head and neck surgeon will continue to see and treat these disorders, and the future will offer improved modalities and materials for the treating surgeon.

Bibliography