

TITLE: CSF Rhinorrhea

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Introduction

Cerebrospinal fluid (CSF) rhinorrhea, no matter the underlying etiology, is the result of an osseous defect at the skull base coupled with a disruption of the dura mater and arachnoid with a resultant pressure gradient leading to the CSF leak. Having knowledge about these leaks, how they occur, and how to treat them is important for multiple reasons, but none as important as the risk of intracranial infection as they persist.

Physiology

Prior to discussing CSF rhinorrhea, basic knowledge of anatomy and physiology of CSF should be reviewed. Roughly 50-80% of daily CSF is made by the choroid plexus while the other 30% is produced by the ependymal surface. CSF production is the result of capillary ultrafiltration occurring through epithelial cells. This is regulated through multiple Na^+/K^+ ATPases. A Na^+/K^+ ATPase on the vessel lumen side takes Na^+ into the cell while another Na^+/K^+ ATPase on the ventricular side moves the Na^+ ions into the ventricle. Water then follows the movement of these ions into the ventricle leading to CSF production. CSF also consists of multiple other ions (K^+ , Mg^{2+} , Ca^{2+} , Cl^- , and HCO_3^-) as well as multiple amino acids and proteins, few cells (polymorphonuclear and mononuclear cells), and glucose (roughly 60-80% of blood glucose). At any one time, roughly 90-150mL of CSF is in circulation. The production rate has been quoted at being around 20mL/hr and 500mL/day.

Causes

Trauma

There are many causes of CSF rhinorrhea and they are classified into different categories. The first category to be discussed is traumatic causes. This category can be further divided into non-surgical and iatrogenic causes. It should be noted that most traumatic/iatrogenic CSF leaks occur in the area of anterior cranial fossa since the dura in this area is tightly adherent to the thin skull base and easily torn with injury to the skull base.

Non-surgical trauma, whether it is blunt or penetrating trauma, accounts for nearly 80% of all CSF leaks. Of all the cases of major head trauma, roughly 2-3% result in a CSF leak. If a skull base fracture is present a CSF leak is seen in 15-30% of cases. These leaks may be either immediate (within 48 hours) or delayed. Nearly 95% of all delayed leaks will manifest within the first 3 months of injury, and are thought to occur as a result of a delayed elevation of intracranial pressure (ICP), lysis of clots in and around the region of injury, resolution of edema, or loss of vascularity with resultant necrosis of soft tissue and bone.

Iatrogenic trauma accounts for 16% of traumatic cases of CSF rhinorrhea. In the past, neurosurgical procedures were the most common causes of surgically produced CSF leaks (resection of pituitary tumors and suprasellar masses). Although the risk of CSF leak with endoscopic sinus surgery (ESS) is reported to be around 0.5%, many more surgeons are utilizing endoscopic techniques in practice today. For this reason, ESS has become the number one cause of iatrogenic induced of CSF rhinorrhea. The most common site of injury during ESS is the lateral cribriform lamella, typically on the right side. Other sites of common injury include the posterior fovea ethmoidalis and the posterior aspect of the frontal recess.

Atraumatic

The next category to be discussed is non-traumatic causes of CSF rhinorrhea. Non-traumatic causes of CSF rhinorrhea account for 4% of all cases of CSF rhinorrhea. This category can be further classified based on the presence or absence of increased intracranial pressure.

High pressure leaks (increased ICP) account for 45% of non-traumatic cases of CSF rhinorrhea. Sustained increased ICP is thought to lead to remodeling and thinning of the skull base that is theorized to be due to ischemia from compression of vessels that eventually leads to the formation of a skull base defect. There are multiple causes of increased ICP with tumor growth and hydrocephalus being two of the more common causes.

Normal pressure leaks represent 55% of non-traumatic cases of CSF rhinorrhea. It is within this category that spontaneous leaks may be placed. It is hypothesized that the cause of spontaneous leaks are the result of physiologic alterations in CSF pressure that lead to point erosions in the skull base resulting in a CSF leak. This theory is based on the fact that it has been shown that every few seconds, elevations in ICP up to 80 mmH₂O occur. Other non-traumatic causes include erosion of the skull base by tumors (nasopharyngeal carcinoma, angiofibroma, inverting papilloma, osteomas) and other osteolytic causes (sinusitis, syphilis, and mucocoeles).

Another category that will be discussed on its own is the congenital causes of CSF rhinorrhea. We are discussing them outside of the other categories because congenital causes may be associated with or without increased ICP. The first, and typically the most common of these defects involve the failure of the closure of the anterior neuropore. This can lead to the herniation of the meninges through the defect (encephaloceles). Another congenital defect that may result in CSF rhinorrhea is a persistent craniopharyngeal canal. This is a vertical midline defect connecting the middle cranial fossa to the sphenoid sinus. Primary Empty Sella Syndrome results in CSF rhinorrhea in a very similar fashion as other spontaneous CSF leaks, but contains a congenital component. Empty Sella Syndrome is the condition in which the sella turcica appears empty on imaging. The primary type is thought to be secondary to a congenital widening of the diaphragma sella plus another event that leads to remodeling of the sellar bone with the formation of a skull base defect in that area. The events that have been recognized are an increased ICP being transmitted through the widened diaphragm causing compression of the pituitary. This is seen with Pseudotumor cerebri, intracranial tumors, and hydrocephalus. The other events include either a rupture or displacement of a cyst into the sella through the widened diaphragm causing compression of the pituitary and resulting in increased pressure within in the sella turcica.

Evaluation

The initial evaluation of a patient presenting with CSF rhinorrhea begins with a good history and physical. The typical history is that of clear, watery discharge from a single nare. There may be an increase in postnasal drip while in the supine position. The patient may also complain of a salty taste in his or her mouth. In the case of headaches, the patient may state that the headache resolves when the leak occurs. Be highly suspicious when there is a previous history of meningitis while the leak has been present.

In most cases, the physical exam is unremarkable. However, some maneuvers can be attempted that may point toward a CSF leak. First, have the patient lean forward and strain. This raises ICP and may illicit a leak. Another way to raise ICP is to compress both jugular veins. The rhinorrhea is typically clear, but if trauma has occurred, it may be mixed with blood. Endoscopic examination of the nasal cavities should be part of every physical examination when CSF rhinorrhea is suspected. Another addition to the physical examination can be determining the presence of the ring or halo sign. When CSF is mixed with blood, it can be placed onto a piece of filter paper. The blood on the paper will separate out from the CSF (central blood with clear ring of CSF). This test is not specific however. Dula et al found that the ring sign occurred when blood was mixed with water, saline, and other mucus.

Laboratory testing is a very important part of making a diagnosis of a CSF leak. There are a number of tests that can be performed, but only one has been deemed a gold standard in determining whether CSF is present or not, and it is the test for beta-2-transferrin. Beta-2-transferrin is a protein that is produced by enzymes only located in the central nervous system. The test requires 0.5cc of fluid, and results can be obtained in as little as 3 hours if the test is readily available. However, in most cases the test is required to be sent out for evaluation, and can take a number of days to return. All specimens should be refrigerated upon collecting. If it is not, the protein will become unstable at room temperature within 4 hours. If it is refrigerated, the sample is good for 3 days.

Glucose testing may be performed, but is not very useful as many things can influence testing. For example, if blood is present the concentration of glucose will be higher resulting in a false positive. The presence of meningitis or other intracranial infections will lower the concentration of glucose in CSF giving a false negative. If no blood is present, one may suspect the presence of CSF when the glucose concentration is $> 30\text{mg/dL}$. If the results show an absence of glucose then the specimen does not contain CSF.

Another method for testing glucose has been by the use of glucose oxidase paper. This paper changes color with glucose concentrations as low as 5 mg/dL . This is not ideal as other fluids in the nasal cavity (lacrimal secretions and nasal mucus) contain a similar concentration of glucose, thus false-positive results are common.

Further testing may include beta-trace protein. This protein is found in CSF, heart, and serum, thus not as specific as beta-2-transferrin in accurately identifying CSF. The protein levels are also altered in other disease states. For example, it is typically elevated in patients with renal insufficiency, multiple sclerosis, cerebral infarctions, and some CNS tumors. If the serum level of beta-trace protein is $< 1.0\text{ mg/L}$, samples with a concentration $> 2.0\text{ mg/L}$ may be considered positive for CSF. However, if the concentration is $< 1.5\text{ mg/L}$, the sample is not likely to contain CSF. If the test is available, it can be performed in 15 minutes.

Imaging

The next step in diagnosing CSF rhinorrhea involves the utilization of imaging. Most surgeons would recommend obtaining high resolution computer tomography (CT) scans in all cases of suspected skull base defects for their ability to detect bony defects. They can also detect the presence of pneumocephalus, soft tissue masses, and hydrocephalus. These images should be 1mm in thickness with axial, sagittal and coronal views. In addition, CT scanning can be combined with the use of intrathecal contrast dye (iopendylate), an imaging modality termed CT cisternography. This study is more invasive, but is more accurate at identifying the location of a CSF leak. CT cisternography has nearly a 100% detection rate when the CSF leak is active. However, with intermittent leaks the rate of detection drops to 60%.

The next imaging modality utilized is magnetic resonance imaging (MRI). This imaging modality is very good at detecting soft tissue abnormalities and distinguishing CSF from other fluid located in a sinus cavity as CSF has high signal intensity on T2 images. MRI can also be combined with intrathecal dye injection to improve accuracy. Overall, this modality is not as good as CT when it comes to detecting bony defects and is much more expensive.

Intrathecal tracers

Nuclear medicine testing has also been utilized in the past to locate the site of a CSF leak, but has fallen out of favor for many reasons. The study is termed radionuclide cisternography. It involves the intrathecal injection of a radioactive tracer (technetium-99, I-131, Indium 111). Prior to this, pledgets are placed into the nasal cavity in areas suspected of being the site of the leak. The dye is injected, scintigrams of the skull are obtained, and then the pledgets are removed and measured for radioactive tracer. The leak site is identified by comparing the results of the scintigrams with the pledgets. However, this study has a lot of drawbacks. First, it almost

always requires an active leak, and even then has been reported at detecting leaks in 70% of cases. If there is an intermittent leak, the ability to pinpoint the area of the leak drops to 30-40%. Second, positioning of the patient can lead to pledgets in areas away from the leak taking up tracer, thus making it more difficult to pinpoint the site of the leak. Third, the radioactive isotope is absorbed into the circulatory system and deposited into normal tissues.

Intrathecal injection of Fluorescein dye is utilized by many surgeons for identifying the area of a CSF leak preoperatively and intraoperatively. Typically, an injection involving a solution of 0.5%-10% Fluorescein dye is performed. The patient is then examined roughly 30 minutes to an hour later with an endoscope. In most cases, the Fluorescein dye can be seen without filters. However, small defects may only leak a very small amount only detectable by filters or black light. In the case of using filters, a yellow filter is placed over the endoscope while a blue filter is placed over the light source. It must be noted that it is extremely important to inject low concentrations of Fluorescein as higher concentrations (>500mg of Fluorescein) can lead to severe side effects that include seizures, pulmonary edema, and even death.

Treatment

Medical

The treatment of CSF rhinorrhea can be classified into conservative management and surgical management. The majority of traumatic CSF leaks respond well to conservative management while spontaneous leaks tend to require surgical correction. In either case, treatment is of extreme importance as the presence of a CSF leak increases the risk of meningitis 10-fold.

Basic, conservative management revolves around bed rest. The patient is placed on bed rest for 7-10 days with the head of bed at 15-30 degrees. The patient is also informed not to strain, cough, or perform heavy lifting. It is reported that with this type of management, 75-80% of all traumatic CSF leaks will spontaneously resolve.

The use of antibiotics in the treatment of CSF rhinorrhea remains controversial. The reason for their use is to prevent intracranial infection (meningitis). However, many studies have shown almost no difference in preventing intracranial infection with or without their use. The fear that many doctors have with their use is the potential to select out more virulent bacterial strains. Brodie et al published a meta-analysis in 1997 reviewing 6 studies and 324 patients with CSF leaks. Two hundred thirty-seven patients were treated with antibiotics while 87 were not treated with antibiotics. Meningitis was reported to have occurred in 2.5% of patients in the antibiotic group (6/237) and 10% of patients in the no-antibiotic group (9/87). Villalobos et al published a meta-analysis in 1998 that reviewed 12 studies and 1241 patients with CSF leaks. Seven hundred nineteen patients were treated with antibiotics while 522 patients were not treated with antibiotics. They found that patients were 1.34 times more likely to develop meningitis without the use of antibiotics when a basilar skull fracture had resulted in a CSF leak. With all causes of CSF leak, patients were only 1.10 times more likely to develop meningitis without the use of antibiotics. For this reason, they recommended not using antibiotics when CSF leaks are present.

When there is increased ICP, diuretic use should be considered. Acetazolamide is a diuretic that inhibits the conversion of water and CO₂ to bicarbonate and H⁺. The loss of H⁺ slows the action of Na⁺/K⁺ ATPases that are responsible for the production of CSF, thus lowering ICP.

Another option to consider is the use of a lumbar drain. In conservative cases, its use should be considered when a leak fails to respond after 5-7 days of conservative management. Continuous drainage is recommended over intermittent drainage as this helps to prevent spikes in CSF pressure. The rate of drainage should be about 10-15cc/hr to prevent side effects such as headaches, nausea, and emesis. There have been cases of patients slipping into comas with too much drainage.

Surgical Treatment

The surgical management of CSF rhinorrhea is categorized into intracranial and extracranial approaches. Intracranial approaches are utilized when there is a comminuted skull fracture with displacement of fragments requiring reduction, extensive skull base fractures, and fractures associated with intracranial hemorrhages or contusions that ordinarily would require craniotomy for treatment. The defects can be repaired by primary closure with or without the use of grafts. Some examples of various grafts utilized include free or pedicled periosteal or dural flaps, muscle plugs, mobilized portions of the falx cerebri, fascia grafts, and many commercial grafts. In addition to this, many surgeons will reinforce these grafts with fibrin glue to provide a better seal. The advantages of an intracranial approach is that it provides direct visualization of the defect, allows for the inspection of the adjacent cerebral cortex for injuries, and allows a better chance of patching a defect, especially in the face of increased ICP. The disadvantages, however, are increased morbidity, increased hospital time, risk of injury to the brain from retraction (hematoma, seizures, cognitive dysfunction, risk of permanent anosmia), and poor visualization of the sphenoid sinus.

The extracranial approach to repairing CSF leaks includes open and closed approaches. For the purpose of this discussion we will focus on the closed approach utilizing endoscopic techniques, as the majority of surgeons utilize this approach as their first line of surgical treatment since studies have shown that the success of repair is > 90%. In addition, an endoscopic approach allows for better magnified and angled visualization, does not require external incisions, and minimizes intranasal mucosal injury.

The key to endoscopic repair of a CSF leak is good visualization and exposure of the defect. Initially, the surgeon must assess whether an encephalocele is present. If an encephalocele is present, it should be cauterized at its stalk with bipolar cautery prior to reduction into the anterior cranial fossa to prevent intracranial hemorrhage. For good exposure, the surgeon should elevate the surrounding mucosa to provide 2-5mm of bone exposure around the defect. Any mucosa remaining in the defect should be removed prior to repair to help prevent future mucocele formation.

There are many types of grafts utilized, but it should be noted that the graft should be roughly 30% larger than the defect to account for post-operative shrinkage. The types of grafting material utilized are cartilage, bone (septum, mastoid tip, middle turbinate), mucoperichondrium,

septal mucosa, turbinate mucosa and/or bone, fascia (temporalis, fascia lata), abdominal fat, and pedicled septal or turbinate flaps. It should be noted that pedicled flaps tend to tint, fold, and contract when utilized.

Grafting techniques can be categorized into overlay, underlay, and combined techniques. In an overlay technique, a graft is placed directly over the defect. In an underlay technique, the graft is placed between the dura and bony defect. The combined technique utilizes both underlay and overlay grafts. In addition to these techniques, most surgeons reinforce the repair with fibrin glue to provide an improved seal. The placement of absorbable (gelfoam) and/or non-absorbable packing can further improve the seal. Most surgeons have moved away from non-absorbable packing since it must be removed post-operatively and may lead to the displacement of the graft when removed. In the face of increased ICP, it is recommended that a multilayered graft be utilized.

The size of the defect also plays a role in the grafting technique utilized. If the defect is < 2mm, the type of grafting technique utilized typically does not make much difference as most techniques will be successful in repairing the CSF leak. If the defect is 2-5mm, one must note whether comminuted bone segments or significant dural injury is present. If they are not present, the use of an overlay grafting technique is sufficient. However, if either is present, one should utilize a composite graft or a separately harvested bone plus mucosa grafting technique where the bone is placed in an underlay fashion while the mucosa is placed in an overlay fashion. If the defect is >5mm, the repair should be performed with a composite graft or separate bone plus mucosa grafting technique as described above.

Post-operatively, the patient should be placed on bed rest with the head of the bed set at 15-30 degrees for 3-5 days. The patient's blood pressure should be maintained at a normal level. The patient should also be placed on stool softeners to prevent straining, and be instructed to not cough, blow his or her nose, and avoid any heavy lifting. Some surgeons will utilize a lumbar drain post-operatively. It is left in place for 3-5 days with a maximum drainage of 10-15cc/hr. If non-absorbable packing is utilized, antibiotics should be given.

Conclusion

In conclusion, CSF rhinorrhea has many etiologies, the most common being trauma. There are many ways to detect the presence of CSF and pinpoint the site of the skull base defect. Treatment may be either conservative or surgical. Remember, CSF rhinorrhea must be recognized and treated appropriately as the risk of intracranial infection is increased 10-fold as it persists.

Discussion by Patricia Maeso, MD of Dr. Gleinser's Grand Rounds presentation on CSF leak 11/20/2009

Did you go into the primary reason why we decide to close these defects? What do you think is the reason we take these patients to the O.R. and try to close these defects?

(Dr. Gleinser): "To prevent infection."

And do you know the risk of meningitis per year? Some studies quote up to 19% per year. So that's really the reason why you take these patients to the O.R. Of course the rhinorrhea is bothersome but really it's the meningitis.

I'm a big proponent of vaccinating these patients with the pneumococcal vaccine. As soon as I know that they have a CSF leak and I'm prepping them for surgery I'll give them a vaccine right there while they're seeing me.

You mentioned bone, you mentioned cartilage, you mentioned mucosa. Fat is also very good to plug up holes. And then over it you can put a thin mucosal graft.

I really like the free graft as well unless it's really something big. The pedicled flaps are a workhorse; they can be misplaced more frequently than your free mucosal graft due to contraction.

I agree with the author you cited that folding and contracture is an issue with that. For fat grafts I just go to the belly. The earlobe is just a little bit tedious. You must know preoperatively how small your defect is. Going to the belly is so much easier plus the quality of the fat is very different. It just doesn't disintegrate as easily and you can get the adipose tissue complete.

I always make sure with a free graft that I always mark it with a marking pen and I paint one side of the free graft so that there's no confusion as to the mucosal side. You can take your free graft from the septum (a full free graft from the septum), you can take it from the floor and that one is really nice. The one that I'm tending to like right now is a free graft off of the inferior turbinate because there's so much that you can get off of it.

I've moved away from using non-resorbable packing though it's really hard and stable and keeps things in place but it might pull things with it. I like re-packing it nicely with Gelfoam.

The patient should be at bedrest for three to five days and should not sneeze or blow their nose. If the patient should decide to sneeze loudly or blow their nose they'll blow their graft out.

Whether we use a lumbar drain depends on how big the site of the defect is, how high the ICP is, the leak flow rate, etc...just make sure you think about these things.

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