“Spontaneous” CSF Rhinorrhoea: Are we missing out?

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ABSTRACT

We carried out analysis of 15 patients with spontaneous cerebrospinal fluid leak presented to our institution in past 2 and half years. In epidemiological assessment we came across co-existing factors like increased body mass index, low or insufficient levels of Vitamin D₃ and serum Calcium, hypothyroidism as plausible confounding agents which are otherwise are not sought upon. All patients were successfully treated by endonasal endoscopic surgical approach except one requiring revision open surgical approach. Along with the surgical treatment patients also received correction of the possible medical factors. Patients have been under follow up for period of minimum 6 months postoperatively and none have recurrence. Thus, it could be suggested that treatment of CSF leak is not and should not be limited to surgical repair only but also encompass finding and correcting the possible causative factors.
INTRODUCTION
Spontaneous cerebrospinal fluid rhinorrhoea though a rare entity, can have devastating complications like meningitis, brain abscess and hence prompt diagnosis and early treatment is necessary.
On basis of etiology CSF rhinorrhoea can be classified into congenital and acquired. Acquired is further classified into traumatic, iatrogenic and neoplastic. Spontaneous CSF rhinorrhoea is thus the one in which no specific cause can be found. There are not many researches currently available to find these etiological factors. Our study has made an attempt to correlate some of these factors like increased body mass index, obstructive sleep apnoea, deficient or insufficient levels of Vitamin D, low serum calcium levels. Though all these factors have no proven relationship to pathogenesis of CSF leak but correcting them can improve long term prognosis, till this relationship is proven by medical research.

Repair of this CSF leak can be done intracranial or extracranial approach. Transcranial repair of CSF leak was first reported by Dandy in 1926 and Wigand was first to perform endoscopic repair of CSF leak in 1981. We have done endonasal endoscopic approach in our patients with a success rate of 93%. This success mainly depends on decreasing the intracranial pressure through surgical, nutritional and medical means.

MATERIAL AND METHODS
We studied 14 patients who visited our outpatient department from July 2015 to January 2018. The most common presenting complaint was watery discharge from nose, which was seen in all patients included in the study. 3 patients also gave history of episodes of meningitis in recent past. Patients with history of antecedent trauma, or nasal surgery in past or congenital skull base malformations were excluded from this study.
A thorough history to rule out recurrent episodes of sneezing, symptoms of obstructive sleep apnoea features of hypothyroidism, and signs of raised intracranial pressure was taken.

All patients underwent diagnostic nasal endoscopy as part of routine procedure. Due to the financial constraints in our institution beta-2 transferrin levels were not done in all cases, though CSF was confirmed in all by CSF analysis. All patients underwent HRCT of paranasal sinuses coronal 1 mm cuts with CT cisternography to locate the site of leak. MRI done in 3 cases helped to confirm the content through the breech.

Patients were also investigated for serum levels of vitamin D3 and Calcium and we also calculated body mass index of all patients. All patients were surgically treated by endonasal endoscopic approach of CSF fistula repair with only one requiring revision open craniotomy approach.

RESULTS
Of the 15 patients who presented to us 10 were females and the age group ranging from 15 years to 60 years with average age of 40.7 years. Out of the 10 females, 6 were peri-menopausal age group correlating with the higher incidence of CSF rhinorrhoea in middle aged females.
4 patients showed active leak on diagnostic nasal endoscopy. Only 5 of the 15 patients fell into normal Body mass index group. 6 were overweight (BMI 25-29.9), 1 class I obese (BMI 30-34.9) and 3 class II obese (35-39.9). Average BMI in the study was 28.75. 2 of the 3 class II obesity patients also had concomitant complaints of obstructive sleep apnoea. Obesity is shown to increase risk of CSF leak.

Though there is a generalized trend of Indian population with insufficient or deficient levels of Vitamin D3, we found Vitamin D3 levels to
be normal (>30 ng/ml) in only 2 patients (14.3%), insufficient (10-30 ng/ml) in 7 (50%) patients and deficient in 5 (35.7%) patients. Average levels of Vitamin D in the study was 17.2 ng/ml. All 5 patients with deficient Vitamin D levels (0-10 ng/ml) and 3 of the 7 patients with insufficient Vitamin D levels (11-30 ng/ml) show reduced serum Calcium too. Average levels of serum calcium in the study were 7.55 mg/dl. We attempted correction of vitamin D levels with Cholecalciferol in dosage of 60,000 IU weekly and found it to be in normalised range in all patients after the completion of 8 weeks of treatment.

One patient has history of epilepsy, two patients were hypothyroid and 3 were receiving regular treatment for hypertension.

Most common site of leak was found to be cribriform plate which was seen in 12 patients (figure 1 medial lamellar leak, Figure 2 Lateral lamellar Leak, Figure 3 Bilateral cribriform Leak.). 1 patient had leak superior to the site of emergence of anterior ethmoidal artery and one from lateral wall of sphenoid sinus (Figure 4. Stenenberg canal leak).

3 patients on radiological assessment showed empty sell sign suggestive of raised intracranial pressure. 2 patients showed presence of encephalocele and 2 patients showed presence of meningoencephalocele. (Figure 5)
The CSF leaks (low pressure) of the patients were managed on the basis of their size and location. In our study, patients with small leaks (<3mm) and leaks located in the medial lamella were repaired using fascia lata graft and tissue glue. We repaired CSF leaks in 4 patients included in our study using this technique. Bigger leaks (>3mm) and leaks in the area of the lateral lamella or junction of the lateral lamella and medial lamella were repaired using bathplug technique using fascia lata graft, fat, tissue glue and Gelfoam. We repaired CSF leaks in 6 patients included in our study using this technique. Large leaks where dura was exposed were repaired using septal cartilage, fascia lata graft, fat, tissue glue and Gelfoam. We repaired CSF leak in 1 patient included in our study using this technique. Defects like meningoceles and meningoencephaloceles were cauterized first and then sealed with fascia lata and tissue glue. We repaired CSF leaks in 4 patients included in our study using this technique.
In one patient who required revision open surgical approach for defect closure we could not find any causative factor suggesting the need for further research in this field. This patient developed a high-pressure leak in the post-operative period, following which a lumbar drain was put. After drain insertion, there was cessation in CSF leak; however patient developed a leak from the opposite side. Following this the patient was referred to the neurosurgeons for further management, wherein leak was closed using open craniotomy approach.

**DISCUSSION**

Ommaya et al have suggested classification for CSF Rhinorrhoea into traumatic and non-traumatic. It is postulated that arachnoid granulations seep into the crevices which may be created by trivial trauma as outpouchings. Over a period of time the continuous pulsations of the arachnoid matter cause the already osteoporotic bone to remodel and erosion occurs thus leading to widening of the cracks from which herniation of meninges or brain matter can occur.

The first step of the diagnosis of CSF leak should be based on the patient’s detailed anamnesis, followed, after clinically suspicion, by laboratory tests for CSF markers. Diagnosis is easier to be made in the case of the patients with recent surgeries or trauma than in other patients. In case of delayed fistulas, there are some difficulties of diagnosis and the CSF leak may appear also years after the trauma. In these cases, it is possible to misdiagnose the leak as a vasomotor or allergic rhinitis. The most frequent symptom in CSF leak is clear, watery nasal discharge from a single nostril, but if the trauma occurred recently, it can be mixed with blood. In the supine position, the volume of nasal discharge may increase. Leakage can also be intermittent due to the accumulation of cerebrospinal fluid in one paranasal sinus and its externalization through the nostril when the head position changes (the “reservoir sign”). The patients may also experience a salty taste. Most of the patients do not have headache, but the presence of this symptom should increase the suspicion of high intracranial pressure and intracranial lesions. It is important if the headache disappears with the leakage. Anamnesis should reveal the presence of meningitis associated with the leak. In some cases, associated symptoms may help us localize the site of the leak. Presence of anosmia is a sign of leak from the anterior fossa and the olfactory area. Optic nerve deficit and visual impairment suggest a lesion of the sellar tuberculum, the posterior ethmoidal cells or the sphenoid sinus. In case of recurrent meningitis, patients should undergo evaluation for the defects that expose the meninges to the upper airways; regardless of the presence or absence of CSF leak.

Laboratory tests are very important for diagnosing CSF leak. From all the tests that have been proposed over the years, only one managed to remain the gold standard in determining the presence of cerebrospinal fluid and that is the test for Beta-2-transferrin. Beta-2-transferrin is a protein of the central nervous system, produced under neuraminidase activity. Because it is not normally found in the nasal secretion, its presence is an indirect marker of CSF rhinorrhoea. For the test, it is necessary to collect a volume of 0.5 ml of fluid. The test is highly sensitive (99%) and specific (97%). Other tests include beta-trace protein, found in the cerebrospinal fluid (35-fold higher levels than serum), heart tissue and plasma, but it has lower specificity than beta-2-transferrin. It may be elevated in cases of renal insufficiency, multiple sclerosis, central nervous system tumors. Nevertheless, the test has the advantage of being quickly to perform, in about 15 minutes, being able to detect very low levels of CSF in the nasal secretion. Other advantages of the beta-trace protein are similar to the Beta-2-transferrin test: non-invasive, repeatable, easy sample collection methods, elevated sensitivity. In the past, glucose testing was performed, because it was easy and it was the most available marker, but it was proved that it has poor sensitivity and specificity. After the confirmation of the CSF rhinorrhoea, the next step consists in identifying its exact site and establishing the
optimal treatment. Localizing the site is, basically, the most important aspect that allows us to expect a successful repair. Imaging investigations are the gold standard in this case. High-resolution computed tomography (CT) examination, with axial, coronal and sagittal reconstructions is the imaging method of choice used for identifying skull base defects, associated with cerebrospinal fluid rhinorrhoea. The images should be 1 mm thick. CT scans can demonstrate the presence of skull base defects after iatrogenic or accidental trauma, as well as various anatomic conditions, hydrocephalus or pneumocephalus and tumoral masses. It is recommended to make CT scans in all cases of suspected bony defects of the skull base. Supplementary, the CT scan may be used in conjunction with intrathecal contrast substance (iophendylate), the imaging modality being termed CT cisternography. The study is much more invasive, but it has greater accuracy in identifying the exact location of a bony defect and a CSF leak. CT cisternography is proved to have almost 100% rate of detection when the patient has an active CSF leak. In cases of intermittent leaks, this rate of detection is hardly 60%. In order to perform this investigation, we must place, under endoscopic control, pledgets in the anterior plate of the cribriform, in the middle meatus or in the sphenoethmoidal recess. When radioactivity is registered through the pledgets, the diagnosis of fistula is sure, although the technique does not provide data about the exact site. Magnetic resonance imaging (MRI), with high specificity for soft tissue lesions and CSF. It is able to differentiate the CSF leak of other intrasinusal fluids, due to the hyperintense signal on T2-weighted imaging characteristic for a CSF leak. MRI may also be used with intrathecal dye administration to improve its accuracy. This imaging modality has a lower specificity than CT in detecting defects of the skull base and the price is much higher. Magnetic resonance imaging cisternography, performed with intrathecal administration of Gadolinium contrast medium, is a method whose accuracy needs to be proved by further studies. Nasal endoscopy has been commonly used as a routine preoperative examination because it is inexpensive, convenient, quick, non-invasive, and painless. To accurately localize the lesion, either the internal jugular vein can be compressed, or the head patient’s head can be bowed to force outflow of CSF during the endoscopy procedure. Conservative treatment of CSF rhinorrhea that occurs immediately after trauma is often recommended for at least 2 weeks before surgical repair because this type of lesion can be self-healing, whether or not dura mater is present in the lesion. However, surgical repair of idiopathic CSF rhinorrhea should be performed as soon as possible after diagnosis. Endoscopic intranasal surgery is the method of choice in the management of CSF leaks, due to its reduced morbidity (no brain retraction, no additional risk of anosmia) and its great field of vision. Nevertheless, this method must identify very precisely the site of the fistula, in order to correctly place the graft. Several different endoscopic approaches have been developed, according to the dural defect localization. The main step of an endoscopic treatment is the good exposure of the dural defect, using also, in low flow cases, intrathecal fluorescein. Initially, if an encephalocele is found, it should be removed carefully. For a good exposure, the surgeon must expose 0.2-0.5 cm of the bone surrounding the defects and the remaining mucosa inside the defect must be excised before repairing, in order to prevent mucocele formation; it also stimulates osteogenesis and it improves graft acceptance. In the current practice, various types of grafts are used, but their size should be no bigger than 30% of the defect dimension. The types of grafting material are cartilage (septum), bone (septal, mastoid tip, iliac crest), septal or turbinate mucosa, fascia (fascia lata, temporalis), abdominal fat, pedicled septal flaps or turbinate flaps. It is important to remind that the pedicled flaps may tint or fold and contract. There are many facts that may influence the option for a certain graft type: defect size and location, level of intracranial
pressure, personal experience and material availability\textsuperscript{34}. The techniques of grafting can be divided into overlay (directly over the defect), underlay (between the dura mater and the bony defect) and combined methods. For underlay techniques the graft is placed between dura mater and skull base. It is crucial to create enough overlap to obtain permeability and to compensate for the postoperative shrinkage of the transplant. The use of fat-plugs that are inserted through the defect and expand above the dura can also be recommended for endoscopic endonasal surgery. They can used to stop CSF-flow while additional measures such as the of overlays or mucoperiosteal flaps are prepared. These fat-plugs can also be stabilized by the addition or cartilage or fascia into the defect for the reinforcement after the graft placement, fibrin glue and autologous abdominal fat are also used. A mucosal fragment from the septum of the middle turbinate may be also placed as an overlay graft. To better seal the defect, fascia (temporalis muscle or fascia lata) offer additional support. After all the grafts are set in place, the defect repair is fixed with Gelfoam® and non-absorbable nasal packing, to increase pressure on the site. Surgeons must pay attention not to obliterate the adjacent sinus ostia. The size of the dura defect is an important parameter when planning the surgical intervention, regarding the number of layers and the type of graft material. When size of leak is less than 3mm, overlay repair is done, when leak is bigger than 3mm it is closed with underlay technique and bathplug technique is used to repair leaks which are up to 15mm in size. During dura obliteration, we must apply the main principle - “watertight closure”. The studies have shown that, when the defect has less than 2 mm, the type of grafting is not important for the success of the intervention. For defects of 2-5 mm, it is recommended to use overlay grafts (mucosal graft or flap), in absence of important dural lesions. If the fracture is comminuted, we should use composite graft. For defects greater than 5 mm, composite grafts or grafts made of mucosa and bone are the method of choice. A multitude of different materials for the closure of skull base defects are available. Most autologous grafts are well suited. The use of autologous materials circumvents all potential dangers of allogenic and xenogeneic transplants such as prion diseases\textsuperscript{35-37}. Many surgeons prefer fascia lata because of its ease of explanation and the relatively big size of transplants that can be obtained. It can be combined with other materials such as cartilage and fat, and its consistency is similar to dura mater. Temporal fascia can also be used although it is thinner than fascia lata. To improve the stability, cartilage obtained from the nasal septum or the ear concha can be added. Bone transplants should be avoided in endoscopic surgery because they are absorbed relatively quickly\textsuperscript{37}. Fat can be removed Para umbilically and can be utilized for obliteration in combination with other materials or as a fat-plug\textsuperscript{38}. Most authors prefer to stabilize transplants and flaps by applying fibrin glue\textsuperscript{38};\textsuperscript{39}. Postoperative care should consist of bed rest, with the head of the bed elevated at 15-30 degrees for 3-5 days. The blood pressure should be kept at a normal value and antibiotic therapy should be administered.

CONCLUSION

- With newer concepts coming into light day by day, spontaneous CSF rhinorrhoea should be more correctly be termed as” non-traumatic” CSF rhinorrhoea.
- As suggested in our study finding the possible causative agents and concurrently correcting them along with surgical intervention is need of the era.
- A thorough history and appropriate investigations can help us identifying the hidden factors like history of trivial trauma, recurrent sneezing, altered levels of Serum Vitamin D and serum calcium also associated comorbid factors like hypothyroidism, raised body mass index, raised intracranial pressure etc. depending on the size, site, content and pressure of the leak the graft materials can be used namely
fascia lata, fat, tissue glue and cartilage tissue.

- Further detailed and long-term studies are needed to associate these factors as causative agents to CSF rhinorrhea.

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