The value of beta trace protein in CSF-leakage detection confirmed by endoscopic fluorescein evaluation

M. Habenbacher[1], D. Sebastnik[1], U. Moser[1], A. Andrianakis[1], P. Kiss[1], Mohammed Alsukayt[2], J. Pock[1], K. Walla[1], E. Maitz[1], P.V. Tomazic † [,1]

[1] Department of Otorhinolaryngology, Medical University of Graz, Austria

[2] Department of Otorhinolaryngology, Security Forces Hospital – Riyadh, Saudi Arabia

Rhinology 62: 6, 766 - 768, 2024
https://doi.org/10.4193/Rhin24.160

Received for publication:
April 11, 2024
Accepted: August 5, 2024

Associate Editor:
Basile Landis

Dear Editor:

Cerebrospinal fluid (CSF) leaks originating from defects within the anterior and middle cranial fossa typically manifest as unilateral clear watery rhinorrhea. Continuous CSF leakage mandates surgical repair due to the risk of meningitis and brain abscess. It can be categorized based on its underlying etiology into traumatic, iatrogenic and non-traumatic CSF leaks. The latter encompasses congenital leaks, leaks resultant from elevated intracranial pressure, and spontaneous leaks without discernible cause [(1)]. The diagnosis of CSF leakage and the subsequent endoscopic repair involve two essential steps: confirmation of the leak's presence and localization of its site [(2)]. Recommended methods for confirming CSF rhinorrhea include testing rhinorrhea fluid for beta-2 transferrin and beta trace protein. After confirmation of the leakage, high resolution (<1 mm slice) computed tomography (HRCT) scan of the sinuses and skull base is recommended for optimal localization of the leak [(3)]. Currently at our department, patients with clinical suspicion of CSF leakage undergo routinely beta trace testing and HRCT. We have used the beta trace protein assay for CSF confirmation for more than a decade due to several reasons: lower cost, rapid turnaround time with sufficient results for sensitivity and specificity (91% to 100% and 86% to 100%, respectively) [(2)]. If the Beta Trace test yields a positive result, endoscopic surgery, with intrathecal Sodium-fluorescein (ITF) evaluation is promptly scheduled. In our experience, ITF allows for accurate localization of CSF leaks, identification of multiple defects, and confirmation of watertight closure at the end of the closure procedure. However, it must also be emphasized, while ITF is a valuable tool for confirming and localizing CSF leaks, it is not always necessary if the leak is clearly identified on HRCT. Many centers may forgo FT in such cases to avoid additional invasive procedures. Furthermore, a negative FT result does not necessarily rule out a CSF leak, as it may indicate a spontaneous closure prior to the procedure.

Recently, we experienced some cases with positive beta trace protein test, who presented during surgery a negative ITF evaluation and no directly visible defect with clear fluid flow. To the best of our knowledge, there are no published data available on the sensitivity of beta-trace protein testing confirmed by intraoperative evaluation of ITF and direct visualization of CSF flow. To fill this gap of knowledge, we performed a retrospective chart review on patients suspicious for CSF leakage with pre-operative positive beta trace protein test, who underwent subsequent ITF evaluation during endoscopic surgery at the Department of Otorhinolaryngology, Medical University of Graz, between January 2010 and December 2020. All cases involved anterior skull base leaks. Lateral skull base defects were ruled out pre-operatively through detailed imaging studies. Our study hypothesis was that the combination of beta trace protein testing, HRCT, and ITF evaluation would provide a reliable protocol for confirming and localizing CSF leaks. Beta-trace test results were considered positive if they exceeded 1.69 mg/L. Sodium-fluorescein was injected intrathecally at a dosage of 0,5 mg per bodyweight via lumbar puncture before surgery. All patients were informed regarding the off-label utilization of ITF and potential associated complications. All patients underwent pre-operative HRCT. If HRCT did not show a clear leak, we proceeded directly to surgery instead of performing routinely an additional magnetic resonance imaging (MRI) because: timely surgical intervention is crucial to reduce the high risks associated with continuous CSF leaks in context with the extended waiting times for an MRI in our region and ITF during surgery provides precise localization and confirmation of leaks in our experience. An additional MRI was performed in some few patients with suspected meningoencephalocele. We recognize that important advancements in imaging technology and increasing experience of radiologists over the study decade may have influenced diagnostic accuracy. However, this study did not specifically evaluate these factors.

Table 1. Characteristics of patients suspected for CSF rhinorrhea with positive beta trace test.

Characteristic	N=28
Age (mean and SD)	47.5 ± 16.2
Sex (female/male)	19/9
BMI	28.8 ± 6.3
OSAS	3 (10.7%)
Cardiovascular risk factors	22 (78%)
Pre-operative meningitis	2 (7.1%)
Positive ITF evaluation	21 (75%)
Visible CSF flow and negative ITF evaluation	1 (3.5%)
No visible CSF flow and positive ITF evaluation	n=5/21 (23.8%)
Beta trace protein sensitivity	22 (78.5%)
Initial surgical success rate	n=15/22 (68.1%)
Time to recurrence (mean, SD and min-max in days)	44 ± 74 (1-208)

Future research should consider these variables to better understand their impact on clinical practice. The study was approved by the institutional ethics committee.
In total, 28 patients with pre-operative positive beta trace testing who underwent subsequent ITF evaluation during nasal endoscopy in this 10 year-period were included in this analysis. Clinical characteristics of the total cohort are depicted in Table 1. Diagnostic details of the individual cases are listed in Table 2. Traumatic leaks were observed in 7 cases (25%), iatrogenic leaks in 5 cases (17.9%), and spontaneous leaks in 16 cases (57.1%).
In 7 out 28 patients (25%), the ITF evaluation was negative and no visible defect as well as clear fluid flow was observed. In one patient (3.5%, Case 13 in Table 2) with negative ITF assay, a visible skull base defect and CSF flow were seen. Five of 21 patients with a positive ITF evaluation presented no directly seen flow of CSF (23.9%). In these cases of positive ITF without precise localization, the surgical team relied on pre-operative imaging and clinical assessment to approximate the likely region of the leak to guide exploration and repair. No complications have occurred as a result of ITF administration. The primary closure success rate was 68.1% (n=15/22). The surgical success rate in the subset of patients with positive ITF evaluation but no directly seen flow of CSF was 60% (3 out of 5 patients). The applied surgical closure technique was in the majority of the cases (91%, n=20/22) a free mucosa flap with/without extra material (fascia lata, fat, fibrin glue and/or Tabotamp® hemostatic layer) in multilayer technique, followed by pedicled flap (9%, n=2/22).
The sensitivity of beta trace protein test confirmed by ITF evaluation and direct visualization of CSF flow was 78.5% (n=22/28), which is comparable to the existing literature [2]. Our study observed a higher proportion of spontaneous leaks and fewer traumatic leaks compared to a large systematic review evaluating 1685 CSF leaks (57% vs. 41% and 25% vs. 30%, respectively) [4]. Advancements in endoscopic sinus surgery and increased medico-surgical knowledge over the past decades likely reduced the proportion of iatrogenic leaks and improved traffic safety features may explain fewer traumatic leaks. In fact, our results are in line with a recent Dutch study [1]. Sodium-fluorescein applied intrathecally was beneficial for localizing the CSF leak in 57,5%, which is modest considering the associated risks. Potential complications of ITF include adverse reactions to fluorescein (e.g. headache, nausea/vomiting, generalized seizures, opisthotonos) and risks from lumbar puncture (e.g. long-term back pain, infection, brainstem herniation, cranial neuropathies, lower limb weakness/numbness) [5]. Topical intranasal applied fluorescein (TIF) represents a non-invasive alternative, offering a much safer modality for patients with promising efficacy results according to a few existing case series [6]. However, future high-quality studies are needed to compare the efficacy and safety of ITF versus TIF in CSF leak localization. In our study, 27.3% (n=6/28) of patients with positive beta trace and HRCT did not have a confirmed leak during surgery, highlighting the limitations of this diagnostic protocol. A recent meta-analysis suggested that MR cisternography (MRC) may offer superior diagnostic accuracy compared to HRCT [7]. Integrating MRC into our diagnostic protocol could potentially reduce unnecessary surgeries by providing more definitive pre-operative CSF confirmation. HRCT and MRC imaging should be probably considered complementary, potentially providing higher accuracy in CSF leak detection when used together. Future research should investigate and compare different diagnostic protocols, such as beta trace + HRCT + ITF versus beta trace + HRCT + MRC + TIF, to identify the most effective and least invasive methods for confirming and localizing CSF leaks.

Authorship contribution

All authors have provided substantial contributions to the conception or design of the work or the interpretation of data for the work. All worked on the draft or revised it critically for important intellectual content. The final version was approved for publishing by all authors. The authors agree on accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

No conflict of interest exists.

Funding

None.

Table 2. Diagnostic details of the individual cases.

	Beta Trace	Leak on HCRT	ITF	Cause
Case 1	Positive	Detected	Positive	Spontaneous
Case 2	Positive	Detected	Positive	Spontaneous
Case 3	Positive	Detected	Positive	Spontaneous
Case 4	Positive	Not detected	Positive	Iatrogenic
Case 5	Positive	Detected	Positive	Trauma
Case 6	Positive	Detected	Positive	Spontaneous
Case 7	Positive	Detected	Positive	Spontaneous
Case 8	Positive	Detected	Positive	Trauma
Case 9	Positive	Detected	Positive	Spontaneous
Case 10	Positive	Not detected	Negative	Spontaneous
Case 11	Positive	Not detected	Positive	Trauma
Case 12	Positive	Detected	Positive	Spontaneous
Case 13	Positive	Detected	Negative	Spontaneous
Case 14	Positive	Detected	Positive	Iatrogenic
Case 15	Positive	Not detected	Positive	Trauma
Case 16	Positive	Detected	Positive	Iatrogenic
Case 17	Positive	Detected	Positive	Spontaneous
Case 18	Positive	Detected	Positive	Spontaneous
Case 19	Positive	Detected	Positive	Spontaneous
Case 20	Positive	Not detected	Positive	Trauma
Case 21	Positive	Not detected	Negative	Spontaneous
Case 22	Positive	Detected	Positive	Trauma
Case 23	Positive	Detected	Positive	Spontaneous
Case 24	Positive	Detected	Positive	Iatrogenic
Case 25	Positive	Detected	Negative	Trauma
Case 26	Positive	Not detected	Negative	Spontaneous
Case 27	Positive	Not detected	Negative	Iatrogenic
Case 28	Positive	Not detected	Negative	Spontaneous

References

1. de Jong WB, Hoogmoed J, Adriaensen GFJPM, Nagtegaal AP, Reitsma S. Aetiology of cerebrospinal fluid rhinorrhoea in a Dutch retrospective cohort from two tertiary referral centres. Rhinology 2024; 62(2): 208-215.
2. Oakley GM, Alt JA, Schlosser RJ, Harvey RJ, Orlandi RR. Diagnosis of cerebrospinal fluid rhinorrhea: an evidence-based review with recommendations. Int Forum Allergy Rhinol 2016; 6(1): 8-16.
3. Georgalas C, Oostra A, Ahmed S, et al. International consensus statement: spontaneous cerebrospinal fluid rhinorrhea. Int Forum Allergy Rhinol 2021; 11(4): 794-803.
4. Psaltis A, Schlosser R, Banks C, Yawn J, Soler Z. A systematic review of the endoscopic repair of cerebrospinal fluid leaks. Otolaryngol Head Neck Surg 2012; 147(2); 196-203.
5. Keerl R, Weber RK, Draf W, Wienke A, Schaefer SD. Use of sodium fluorescein solution for detection of cerebrospinal fluid fistulas: an analysis of 420 administrations and reported complications in Europe and the United States. Laryngoscope 2004; 114: 266-272.
6. Romeo D, Ng JJ, Fritz C, De Ravin E, Suresh N, Harris J, Rajasekaran K. Evaluating the efficacy of topical intranasal fluorescein for localizing csf rhinorrhea: a systematic review. J Craniofac Surg. 2023; 34(3): e326-e329.
7. Xie M, Zhou K, Kachra S, McHugh T, Sommer DD. Diagnosis and localization of cerebrospinal fluid rhinorrhea: a systematic Review. Am J Rhinol Allergy 2022; 36(3): 397-406.

Alexandros Andrianakis M.D. Ph.D.
Department of Otorhinolaryngology
Medical University of Graz
Auenbruggerplatz 26
8036 Graz
Austria

Tel: +43 (316) 385 - 81359
E-Mail: alexandros.andrianakis@medunigraz.at