Incidence of Occult Cerebrospinal Fluid Fistula During Paranasal Sinus Surgery

Gregor Bachmann, MD; Uta Djenabi, Cand Med; Markus Jungehülsing, MD; Hela Petereit, MD; Olaf Michel, MD

Objective: To determine the incidence of occult cerebrospinal fluid fistulas after endoscopic paranasal sinus surgery.

Design: Prospective diagnostic test study with a 6-month follow-up in case of cerebrospinal fluid detection.

Setting: Tertiary care hospital.

Subjects: The study population comprised 69 patients undergoing routine endoscopic paranasal sinus surgery. Patients with an obvious intraoperative or postoperative cerebrospinal fluid fistula were not included.

Intervention: Analysis of 112 samples from intraoperative applied tamponades and of 69 serum samples using a nephelometric research assay for β-trace protein (prostaglandin D synthase).

Main Outcome Measures: Incidence of occult cerebrospinal fluid fistula during endoscopic paranasal sinus surgery as indicated with the help of a test for β-trace protein; at least a 6-month follow-up of patients with an occult cerebrospinal fluid fistula; and relation of occult cerebrospinal fluid fistula with surgical experience of the surgeon.

Results: β-Trace protein was found in ethmoid roof samples from 2 patients, giving an incidence of 2.9% for occult cerebrospinal fluid fistula. Both patients were operated on by very experienced surgeons. Signs of a cerebrospinal fluid fistula were not found at follow-up at least 6 months after surgery.

Conclusions: Nephelometric β-trace protein assay is a highly sensitive method to detect otherwise unobserved cerebrospinal fluid fistulas. The clinical course of the 2 patients with an occult cerebrospinal fluid fistula indicated the possibility of an uneventful follow-up of patients with small fistulas.


Patients with a cerebrospinal fluid (CSF) fistula are at risk to develop meningitis, which is still a life-threatening condition. With a traumatic CSF leak, the cumulative risk to develop meningitis exceeded 85% after 10 years, and, in spite of extensive antibiotic treatment, the mortality rate of bacterial meningitis was reported to be 25% to 50%. Cerebrospinal fluid fistulas occur as congenital defects, after head trauma and surgery, because of tumor invasion, or without any obvious reason. A rare cause of CSF fistula are bony defects due to arachnoid granulation tissue. Cerebrospinal fluid leaks are a well-known complication of paranasal sinus surgery. However, the incidence of an unobserved, intraoperative CSF fistula—termed occult CSF fistula—is not presently known. Furthermore, it is not known whether an occult CSF fistula will finally lead to a clinical obvious permanent fistula.

Recently, a new nephelometric research assay was introduced for the quantification of β-trace protein (β-TP), which is an ideal immunological marker for the detection of traces of CSF fluid. β-Trace protein belongs to the lipocalin family of proteins with carrier and enzymatic functions and is produced in the meninges and choroid plexus and, to a lesser extent, in astrocytes. The physiological role of the protein is not known. In 1993, after the determination of amino acid sequence, it was shown that β-TP is identical with prostaglandin D synthase (EC 5.3.99.2, as classified by the Enzyme Commission). β-Trace protein showed a CSF/serum ratio of 33, which is the highest of the CSF-specific proteins presently known. For the detection of CSF fistulas, β-TP showed high predictive values in 98 subjects. The aims of the present study were to present a new β-TP nephelometric research assay as a tool for clinical research and to investigate the incidence of occult CSF fistula in patients...
undergoing routine paranasal sinus surgery in a prospective setting.

**METHODS**

**PATIENTS AND SURGICAL PROCEDURE**

Sixty-nine patients were enrolled between 1998 and 2000. The mean ± SD age was 47.9 ± 13.0 years, and the sex distribution was 27.5% women and 72.5% men. Patients with previous surgery and patients with fungal paranasal sinus disease were included. Patients with a clearly visible CSF leakage during surgery were not included. The indication for surgery was chronic paranasal sinus disease with or without nasal polyposis. All patients underwent endoscopic paranasal sinus surgery according to the Messerklinger or Wigand technique. Thirteen patients underwent unilateral procedures. Bilateral procedures were performed in 56 patients. Highly and less experienced surgeons were included, but all surgeons had at least 2 years of otorhinolaryngologic surgical training.

**SAMPLING**

Raucocel (Rauscher, Germany) sinus packs were placed at the ethmoid roof at the end of the surgical procedure. After the Raucocel packs were inserted, they were soaked with doxycycline solution to prevent local postoperative infection. At the first postoperative day, a serum sample was taken, and at the second postoperative day, the sinus packs were removed. Fluid samples were obtained by pressing the sinus packs. The samples were centrifuged at 4000 rpm for 5 minutes and were kept at −40°C before investigating for β-TP nephelometry.

**FOLLOW-UP**

Patients with a positive or a suggestive β-TP result were followed up at least 6 months after surgery. A nasal endoscopy was performed, and a sinus pack tamponade was used to collect a fluid sample. Under local anesthesia, sinus packs were placed at the ethmoid roof on both sides. The sinus packs were left in place for 3 hours. After removal, the sinus packs were pressed, and the fluid samples were analyzed for β-TP.

**β-TP NEPHELOMETRIC ASSAY**

For quantitative determination of β-TP, a newly developed nephelometric research assay, N Latex β-TP (Dade Behring, Liederbach, Germany), was used. N-Latex β-TP is a lyophilized reagent for the Behring Nephelometer Analyzer (Dade Behring). Polystyrene particles coated with immunoaffinity-purified polyclonal antibodies from rabbit against human β-TP were agglutinated in the presence of β-TP. The increase in light scattering caused by agglutination was measured by laser absorption as described elsewhere. The sample volume was 5 µL. The analytical imprecision of the assay was 2.3% to 6.5%. The detection limit for the undiluted sample was 2.5 µg/L. The nephelometric assay offers results after 20 minutes.

In accordance with recently published data, samples with a β-TP concentration of 6 mg/L or higher were reported as positive, indicating the presence of CSF. A result lower than 3 mg/L was defined as negative for CSF traces. A result between 3 and 6 mg/L was suggestive of CSF.

**CALCULATION OF CORRECTED β-TP RESULTS**

Kleine and coworkers found that a small amount of β-TP binds to sinus pack materials. Because of this, the results might be up to 30% lower compared with samples, which were collected without sinus packs. Therefore, the β-TP results from all Raucocel sinus packs were corrected using the formula x = (y × 100):70.

**RESULTS**

The quantitative data are given in the Table. Calculating the incidence in 69 subjects, we found an occult CSF fistula in 2.9%. When calculating the incidence on the basis of 112 sinus packs, we found an occult CSF fistula in 2.7% (3 positive samples).

The average value of β-TP in serum was 0.69 ± 0.33 mg/L. As usual, all sinus packs contained a large amount of serum, blood, and doxycycline solution. Three samples from 2 patients showed elevated β-TP results. Also, when taking into account that up to 50% of β-TP was bound to the sinus pack material, the results of the sinus packs showed presence of CSF in the same 2 cases.

**CASE 32**

A 64-year-old patient underwent a revision paranasal sinus surgery because of recurrence of polyposis nasi. The bony structures showed no anatomic malformation, as demonstrated by a high-resolution computed tomographic scan of the coronal plane. Surgery was performed under general anesthesia by one of the most experienced surgeons of the department. The procedure was in accordance with the Wigand technique. The intraoperative and postoperative course was unremarkable. There were no headaches, no fever, and no signs of rhinorrhea. Analysis of samples from the sinus packs for β-TP indicated clear evidence of CSF on both sides. Therefore, the patient was followed up 9 months later. The patient had no complaints. He did not develop meningitis, and signs of rhinorrhea were not found. The β-TP results at follow-up were 0.5 and 0.3 mg/L, indicating no traces of CSF.

**CASE 33**

A 53-year-old patient presented with polyposis nasi. She had no previous surgery. Again, surgery was performed by one of the very most experienced surgeons of the department under general anesthesia. The fluid samples from the paranasal sinus packs showed β-TP values of 3.1 and 1.7 mg/L, suggesting the presence of CSF on one side. According to the study protocol, the patient was followed up 6 months after surgery. The patient did not have any complaints, and she did not develop meningitis. Signs of rhinorrhea or clinical signs of a CSF fistula were not present, and the β-TP results of the sinus packs at follow-up were not suggestive for the presence of CSF traces.

**COMMENT**

The verification of a CSF fistula can be difficult because of several aspects. Patients with a CSF fistula might present...
ternography, In-DTPA (indium III diethylenetriamine pentaacetic acid) radionuclide cisternography, and magnetic resonance imaging offer information about the localization of a CSF fistula, but are not suitable for a prospective clinical study. The β_{2}-transferrin assay is available only at a few centers and requires a laboratory workup of at least 3 hours. Other laboratory methods to detect CSF traces failed to gain clinical relevance. The electronic nose offers a new method to differentiate between serum and CSF, but it is unclear whether it is possible to detect CSF traces in serum samples.

We chose the new β-TP assay because it offers high predictive values in the detection of CSF fistulas. Also, small sample volumes are sufficient, and the method is not invasive. The costs are low, and the results are available after 20 minutes when using the nephelometric assay. Furthermore, quantitative data are well suited for a screening test.

A prospective study investigating the incidence of CSF fistula after endoscopic paranasal sinus surgery is lacking at present. From a retrospective study, the incidence of postoperative CSF fistulas was reported to be less than 1% in 800 patients. Solomon et al investi-
They reported that all samples did not contain β2-transferrin and thus excluded the theorem of extracranial drainage of CSF.38

Sinus packs removed at the second day after surgery contain a large amount of serum and blood. It might be difficult to detect CSF traces in these packs. However, from our results, occult CSF fistulas occur during endoscopic paranasal sinus surgery with an incidence of 2.9%. We therefore believe that the β-TP test is the most sensitive method to trace CSF.

The experience of the surgeon does not seem to correlate with the complication of an occult CSF fistula. In contrast, the 2 patients with an occult CSF fistula were both operated on by very experienced surgeons.

Furthermore, we could not find data in the literature giving information about the prognosis of occult CSF fistulas. The results of the present study indicate that an intraoperative occult CSF fistula might close spontaneously during the postoperative healing process. In the 2 patients with an occult CSF fistula, the postoperative course and the 6 months’ follow-up were uneventful. However, the surgeon must be aware of the possibility of an occult CSF fistula, and a close, long-term follow-up of patients with a proven occult CSF fistula is advisable.

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Corresponding author: Gregor Bachmann, MD, Oreneshals-avdelingen, Universitetssykehuset i Nord-Norge, N–9038 Tromsø, Norway (e-mail: gregor.bachmann@unn.no).

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