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Chapter 6

Risk Factors for Meningitis After Transsphenoidal Surgery

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ABSTRACT

To evaluate possible risk factors for meningitis, we retrospectively reviewed 228 transsphenoidal operations (in which a standard regimen of amoxicillin prophylaxis was used) for sellar pathology. The incidence of meningitis was 3.1% (seven of 228 cases). Cultures of preoperative specimens from the anterior nasal vestibule in three of seven patients yielded *Staphylococcus aureus*, but none of these patients developed *S. aureus* meningitis. Two of three patients with significant preoperative paranasal sinus abnormalities developed meningitis compared with only five of 225 patients without significant paranasal sinus abnormalities ($P < 0.005$). Three of 22 patients with intraoperative cerebrospinal fluid leakage developed meningitis compared with four of 206 patients without intraoperative CSF leakage ($P < 0.05$). Six of seven patients with postoperative CSF rhinorrhea and only one of 221 patients without postoperative CSF rhinorrhea developed meningitis ($P < 0.0001$). In conclusion, postoperative CSF leakage is an important risk factor of meningitis after transsphenoidal surgery. Cultures of preoperative specimens from the anterior nasal vestibule did not have any predictive value in our study.

INTRODUCTION

Transsphenoidal surgery is presently the treatment of choice for lesions in the sellar region. It has replaced craniotomy in most cases, because of the absence of visible scars and because of lower morbidity and mortality rates. Disadvantages of the transsphenoidal approach are a restricted field of surgery, generally absent visualization of the optic nerves, and the risk of postoperative CSF rhinorrhea and meningitis (1). The role of antimicrobial prophylaxis in neurosurgery has been discussed extensively (2-7). In a recent review, TSS has been classified as a clean-contaminated procedure, since the air-filled sphenoidal sinus is crossed; therefore, prophylaxis has been recommended (2). However, meningitis still occurs as a complication of TSS, with its incidence ranging from 0.4% to 9% (8-14). We retrospectively reviewed the results of 228 consecutive transsphenoidal operations in which a standard regimen of amoxicillin prophylaxis was used to evaluate possible risk factors for meningitis. We also studied the value of preoperative nasal cultures in relation to the pathogens isolated from CSF.

Patients and Methods

The medical records of all patients who underwent TSS in our hospital between January 1988 and December 1994 were reviewed. All operations were performed by the same two neurosurgeons. The preoperative workup included culture of a swab from the anterior nasal vestibule for isolation of *Staphylococcus aureus* and other pathogenic microorganisms and roentgenography of the paranasal sinuses. After TSS, a nasal tampon of oxytetracycline/mL, 10,000 U of polymyxin B/mL, and 5 mg of hydrocortisone/mL (Terra-Cortril, Pfizer, Rotterdam, the Netherlands) was inserted. The gauzes were removed after 6 postoperative days. All patients received a standard regimen of amoxicillin prophylaxis: 750 mg orally every 8 hours during the day before the operation, a single 1000-mg intramuscular injection on the morning of the operation, and subsequently 750 mg orally every 8 hours until the sixth operative day. Operation records were checked for intraoperative CSF leakage. Postoperative CSF rhinorrhea was established by the presence of 2-transferrin and/or glucose in the nasal fluid. Onset, duration and management of CSF rhinorrhea were recorded. Cases of meningitis were identified according to the definitions of nosocomial infections of the Centers for Disease Control and Prevention (15). Detailed information on clinical presentation, cultures and chemistry analysis of CSF, treatment, and outcome was recorded. The following risk factors were evaluated: diagnosis of TSS, positive culture of preoperative nasal swab specimen, preoperative CSF leakage, postoperative CSF rhinorrhea, and use of lumbar drainage. Statistical analysis was performed by using Fisher's exact test.

RESULTS

Incidence of Meningitis

In the 7-year period, 228 transsphenoidal operations were performed; the indications of these procedures are listed in table 1. The patients with Nelson's syndrome were eucortisolemic and received replacement therapy with hydrocortisone (20 – 30 mg daily). Seven operations (3.1%) were complicated by meningitis (table 2). One patient (patient 1) had undergone TSS 5 years previously, and this operation had also been complicated by meningitis due to *S. aureus*. Four (7.5%) of 53 patients with Cushing's disease developed postoperative meningitis compared with three (1.7%) of 175 patients treated for other reasons ($P = 0.05$).

Table 1. Diagnostic reasons for transsphenoidal surgery during a 7-year period.

Diagnostic reason	No. of cases
Cushing's disease	53
Acromegaly	77
Prolactinoma	8
Non-functioning adenoma or gonadotropinoma	70
Nelson's syndrome	4
Other pathology in the sellar region	16
Total	228

Clinical Presentation and Outcome

The average interval between TSS and the onset of clinical symptoms of meningitis was 12 days (range 4 – 20 days). One patient had already been discharged from the hospital when she presented with a convulsion as the first symptom of meningitis. In one patient (patient 3), meningitis developed while the patient was still receiving antimicrobial prophylaxis. In patients 1-6, at least two of the following three symptoms were present: fever, meningism, and headache. In one patient (patient 7), paralysis of the hands was the only presenting symptom. All patients completely recovered after appropriate antibiotic therapy.

Microbiology

Cultures of CSF specimens from five patients (patients 1, 3, and 5 – 7) yielded gram-positive bacteria (table 2). These organisms were all susceptible to amoxicillin, except for a penicillin-resistant *S. aureus* isolate from patient 7. Culture of a CSF specimen from one patient (patient 2) yielded *Haemophilus influenzae*. CSF cultures for one patient (patient 4) remained negative, but this patients clinical presentation and high CSF WBC count met the criteria for meningitis.

Nasal Swab Specimens

Preoperative swab specimens from the anterior nasal vestibule in 211 (92.5%) of 228 patients had been obtained; cultures of 61 (28.9%) of the specimens were positive. Cultures of 54 (25.6%) of the 211 nasal swab specimens yielded *S. aureus*; 17 (31.5%) of 54 isolates were penicilline-susceptible, and 31 (94%) of 33 isolates were tetracycline-susceptible. Cultures of preoperative nasal swab specimens from three of seven patients who developed meningitis all yielded *S. aureus*. Only the isolate from patient 4 was susceptible to amoxicillin. *S. aureus* was not cultured from CSF specimens from any of these three patients during the episodes of meningitis. The two patients with *S. aureus* meningitis had negative cultures of nasal swab specimens yielded *Streptococcus pyogenes* (2 patients), *Proteus mirabilis* (3), *Streptococcus pneumoniae* (1), *Haemophilus parainfluenzae* (1), *H. influenzae* (1), *Klebsiella pneumoniae* (1), *Enterobacter aerogenes* (1), and *Morganella morganii*(1).

Paranasal Sinus Abnormalities

Roentgenograms of paranasal sinuses in 176 (77%) of 228 patients were obtained preoperatively. The paranasal sinuses in 148 (84%) patients were normal. Of the 28 patients with abnormal roentgenograms, only three had clinically significant abnormalities and received treatment for sinusitis; treatment included antibiotics for all three patients and infundibulotomy for one patients (data not shown). TSS was performed 8 to 16 days after this treatment. Two of these three patients (patients 1 and 2) developed meningitis ($P < 0.005$) (table 2).

CSF Leakage

Intraoperative CSF leakage was observed in 22 patients (9.6%). Three of 22 patients with CSF leakage developed meningitis compared with four of 206 patients without intraoperative CSF leakage ($P < 0.05$). To prevent CSF rhinorrhea and fistula formation, nine of 22 patients underwent lumbar drainage immediately after TSS. None of these patients developed meningitis. Of the 13 patients who did not undergo immediate lumbar drainage, three (23%) developed meningitis. Postoperative CSF rhinorrhea occurred in seven patients. In six of these seven patients, meningitis developed. Only one of 221 patients without postoperative CSF rhinorrhea developed meningitis ($P < 0.00001$).

When CSF rhinorrhea occurred, lumbar drainage could not prevent the development of meningitis (patients 1, 2 and 7). One patient (patient 4) developed meningitis without any signs of intra- or postoperative CSF leakage. Postoperative CSF rhinorrhea in six patients was treated by lumbar drainage. Surgical closure of the CSF fistula in one patient (patient 5) was performed later in the course of meningitis.

Table 2. Characteristics of seven patients with meningitis after transphenoidal surgery with amoxicillin prophylaxis

			Patient no.				
Characteristic	1	2	3	4	5	6	7
Diagnosis	Nelson's syndrome	Cushing's disease	Cushing's disease	Macro prolactinoma	Cushing's disease	Nelson's syndrome	Cushing's disease
Preoperative							
Abnormalities on paranasal sinus roentgenogram	+	+	+	-	-	-	-
Nasal swab culture	-	-	-	Staphylococcus aureus	S.aureus	-	S.aureus
Intraoperative CSF leakage	-	+	+	-	-	-	+
Postoperative CSF rhinorrhea	+	+	+	-	+	+	+
Day of onset of CSF rhinorrhea	11	13	25	-	6	11	8
Duration of lumbar drainage (d)	11-24	14-28	29-38	-	Surgical closure on day 15	11-18	11-18
Day of onset of symptoms	12	17	20	8	7	4	16
<u>Clinical presentation</u>							
Fever	+	-	+	+	+	+	-
Meningism	+	+	+	+	-	+	-
Headache	+	+	+	+	+	+	-
Other	Photophobia	-	Convulsion	-	Vormitin, hemiparesis	-	Paralysis of hands
CSF findings (at the time of diagnosis)							
WBC count (/mm ³)	2.288	224	4*	1.777	291	4.555	144
Glucose level (mg/dL)	ND	110	112	ND	59	23	63
Protein level (mg/L)	ND	250	750	ND	1.620	1.590	620
Gram staining result	Gram-positive cocci and rods	-	-	-	-	-	-
Culture result	S. aureus	Haemophilus influenzae	Streptococcus Sanguis II	-	Enterococcus species	S. aureus	Sterptococcus intermedius
Initial therapy	Floxacillin, cefotaxime	Floxacillin, cefotaxime	Amoxicillin/ clavulanic acid	Floxacillince-fotaxime	Cefuroxime, chloramphenicol	Floxacillin, cefotaxime	Floxacillin, cefotaxime
Outcome	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful

DISCUSSION

TSS for treatment of pituitary lesions continues to be a safe and effective procedure (1). However, this method may be complicated by meningitis. The incidence of meningitis in our series was 3.1%, which is in concordance with rates reported in the literature (8-14). All of our patients with meningitis were cured following appropriate antibiotic therapy.

As in other studies, our study had an overrepresentation of patients with Cushing's disease who developed meningitis after TSS (four of seven patients) (16). This overrepresentation may be explained by the fact that these patients have some degree of impaired immunity (17). Since two of our three patients with clinically significant sinus abnormalities on roentgenograms developed meningitis, we would recommend the inclusion of a routine roentgenogram of the paranasal sinuses in the preoperative workup for TSS. To avoid contamination of the operative field by micro organisms, sinusitis should be treated adequately, and TSS should be postponed for at least 4 weeks. When urgent TSS is required, appropriate antibiotic therapy should be continued for a longer period after the operation.

The bacterial flora of the operative field might be important in the pathogenesis of post surgical meningitis. However in our study, cultures of preoperative nasal swab specimens were not reflective of the organisms isolated from CSF specimens from patients developing meningitis. Studies of other groups of patients with wound infections have had similar results(18). Therefore, we do not advocate routine culturing of preoperative nasal swab specimens before TSS. The presence of *S. Aureus* in 25.6% of cultures of nasal swab specimens from our patients is similar to findings of other studies (12). Our prophylactic regimen would not have been expected to prevent meningitis due to the usual β -lactamase-positive strains of *S. aureus*. Nevertheless, since two of the four patients who were not colonized preoperatively developed meningitis due to *S. aureus*, the possibility of utilizing a prophylactic antibiotic formulation that is active against *S. aureus* may be considered.

In the literature, the postoperative interval to the appearance of the first symptoms varied from 1 to 42 days (12,19,20). One case of meningitis associated with CSF leakage that occurred 9 years after TSS was reported (6). In a recent study by HaileMariam et al (11), intraoperative contamination through a CSF leak was proposed as the mechanism of meningitis following TSS. In their study, meningitis developed within 4 days after TSS, while the patients were still being treated with prophylaxis for staphylococcal infection.

In our study, the first clinical symptoms of meningitis developed an average of 12 days after TSS. Therefore, in most patients, bacterial contamination of CSF must have taken place >6 days after TSS. In three patients, intraoperative CSF leakage had been observed, but meningitis developed only on the 16th, 17th and 20th postoperative day, respectively. Intraoperative introduction of bacteria is not compatible with this interval. Our data strongly suggest that infection occurred

via a CSF leak in the postoperative period rather than intraoperatively. Once postoperative CSF rhinorrhea had been observed, patients were at a significantly higher risk for meningitis, despite adequate lumbar drainage. However, it seems that immediate lumbar drainage prevented postoperative nasal liquorrhea and consequently meningitis.

Previously, TSS-associated meningitis was reported to be predominantly caused by gram-negative bacteria (11,14). Alteration of the mucosal flora to gram-negative species during prolonged hospitalisation and prophylactic use of antibiotics might explain this phenomenon (20,21). In contrast, cultured CSF samples from five of our seven patients with meningitis yielded gram-positive bacteria, and no nosocomial gram-negative pathogens were found.

CSF leakage with meningitis has been described in association with skull fracture with CSF fistula and in association with other neurosurgical procedures, including surgery for acoustic neuroma (2,19,22-24). The goal of antimicrobial prophylaxis in the procedures, as in TSS, should be the maintenance of the sterility of CSF when the arachnoidea is ruptured (3,25). However, this goal was not reached with our antibiotic prophylaxis, since amoxicillin doses were not high enough for sufficient CSF concentrations. Alternatively, resistant strains might emerge because of the selection effect of antimicrobial prophylaxis. A recent consensus report did not recommend antimicrobial prophylaxis for patients with CSF leakage, because no prospective, randomized clinical trials have been performed (2). Because of the fact that our study was not placebo controlled, we cannot draw conclusions on the efficacy of our regimen for antibiotic prophylaxis. Perhaps the local application of polymyxin B and tetracycline, in addition to systemic amoxicillin, prevented the emergence of gram-negative organisms causing meningitis.

In conclusion, postoperative CSF leakage is an important risk factor for meningitis after TSS. Cultures of preoperative nasal swab specimens did not have any predictive value in our study. Preoperative roentgenograms of the paranasal sinuses seem mandatory. Still, prospective studies are needed to determine preoperative prophylaxis for patients undergoing TSS, especially those with postoperative CSF leakage.

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