

Clinical Characteristics of *Streptococcus Pneumoniae* Meningoencephalitis after Transsphenoidal Surgery: Three Case Reports

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Abstract

We report three extremely rare cases of *Streptococcus pneumoniae* meningoencephalitis (SPM) after transsphenoidal surgery (TSS). Between 2004 and 2010, we experienced three cases of severe SPM after surgery out of 1,965 patients undergoing TSS (0.15%). The three cases included a 4-year-old boy with a large cystic craniopharyngioma, a 40-year-old man with a non-functioning pituitary adenoma, and a 55-year-old man with acromegaly. The similarity among these SPM patients was that severe clinical events occurred suddenly 1–2 months postoperatively without any history of sinusitis or pneumonia. Despite intensive care these patients notably had residual neurological sequelae. In no case was rhinorrhea associated with SPM. It should be noted that SPM was not detected from bacterial cultures of the sphenoidal sinus mucous membranes (BCSM) obtained during TSS in two of the patients examined. Severe postoperative SPM can occur suddenly without cerebrospinal fluid (CSF) leakage within 2 months after surgery and requires emergency treatment. Reduced resistance to infection may play a role in the occurrence of SPM in our three patients. Our study indicates that BCSM is not useful for predicting postoperative meningitis.

Key words: complications, meningoencephalitis, pituitary tumors, *Streptococcus pneumoniae*, transsphenoidal surgery

Introduction

Bacterial meningitis is a severe complication of transsphenoidal surgery (TSS) for pituitary tumors^{1–3)} with an incidence ranging from 0.4% to 9%.³⁾ For instance, Van Aken et al. mentioned an incidence of 3.1% after TSS (7 of 228 cases)³⁾ and described five gram-positive bacteria including two species of *Staphylococcus aureus*, and one species each of *Streptococcus (Str.) sanguis*, *Str. intermedius*, and *Enterococcus* species³⁾. In contrast, only two of 316 consecutive patients who underwent TSS or extended TSS between January 2006 and July 2007 (0.63%) at our institution were diagnosed with postoperative meningitis, demonstrating a lower incidence of postoperative meningitis in our department compared with others.^{2,3)} However, meningoencephalitis due to *Str. pneumoniae*

is considered extremely rare, and to our knowledge only one patient has been reported in the English literature with this disease.¹⁾ Therefore, the clinical characteristics of *Streptococcus pneumoniae* meningoencephalitis (SPM) associated with TSS remain to be elucidated. We have experienced three cases of SPM after TSS between 2004 and 2010, which accounts for 0.15% of the 1,965 cases of TSS performed for the treatment of various types of pituitary diseases at Toranomon Hospital, including pituitary adenomas, craniopharyngiomas, and Rathke's cleft cysts. Here, we report these three cases of SPM to clarify the clinical characteristics of postoperative SPM after TSS.

Case Report

I. Case 1: Large cystic craniopharyngioma, 4-year-old male (Fig. 1A, B)

The patient complained of visual disturbance with impaired eye movements. Magnetic resonance (MR) imaging

showed a large, cystic, dumbbell-shaped craniopharyngioma. He underwent complete tumor excision via extended TSS in October 2009. Cerebrospinal fluid (CSF) leakage was unavoidable during surgery due to the extended approach, and a large dural defect was reconstructed with a dural fascia graft followed by subcutaneous adipose tissue and fibrin glue to prevent postoperative CSF leakage.⁴⁾ The patient received prophylactic antibiotics [cefazolin sodium (CEZ)] for 7 days. The patient was necessary refilled hydrocortisone, levothyroxine, and desmopressin after surgery. The postoperative course was unremarkable, there was no CSF leakage, and the patient was discharged 1 month after surgery with hormonal replacement for panhypopituitarism with diabetes insipidus. No laboratory data suggested inflammation at the time of discharge. However, 1 month after discharge (i.e., 2 months after surgery) the patient demonstrated high fever (up to 39°C) and generalized convulsions. He was diagnosed with SPM due to his clinical symptoms (e.g., high fever, neck stiffness) and CSF examination (cell counts: 2,530 μ L, protein: 134 mg/dl, glucose: 12 mg/dl), which included a bacterial culture.

On the following day the patient was in critical condition with a severe disturbance of consciousness and convulsions. The patient recovered after intensive treatment with appropriate antibiotics, but he suffered cortical blindness secondary to an occipital infarction due to arterial vasculitis after SPM.

II. Case 2: Non-functioning adenoma, 40-year-old man (Fig. 1C)

The patient had a past history of repeat TSS at another hospital for the treatment of a non-functioning pituitary adenoma. During the second surgery severe intraoperative bleeding from the cavernous sinus occurred which resulted in severe postoperative anemia [hemoglobin (Hb) was reduced to 6.8 g/dl]. A repeat TSS was performed in July 2004 at Toranomon Hospital, and the tumor was completely removed without any intraoperative CSF leakage. He received prophylactic antibiotics (CEZ) for 3 days, and his postoperative course was uneventful. For this patient, postoperative hormonal replacement was not required. He was then discharged 10 days after surgery with slight anemia (Hb: 11 g/dl). The patient suddenly complained of severe headache 2 weeks after discharge (1 month after TSS) with a high fever followed by generalized convulsions. He was taken to the hospital by ambulance 2 days after the onset of high fever. He was comatose, and although a computed tomography (CT) scan did not show pneumocephalus, it did demonstrate diffuse brain swelling with multiple infarctions. Subsequent bacterial culture of the CSF revealed SPM (additional data from the CSF are not available). The patient died 2 weeks later despite intensive treatment for SPM. Neither CSF leakage nor pneumocephalus were found during the course of his

meningoencephalitis. Bacterial cultures of the sphenoidal sinus mucous membrane (BCSM) performed at Toranomon Hospital confirmed no *Str. pneumoniae*, although both *Staphylococcus* species and *Klebsiella pneumoniae* were detected in the membranes.

III. Case 3: Acromegaly, 55-year-old man (Fig. 1D, E)

This patient, a blue-collar worker, was diagnosed with acromegaly based on clinical and endocrinological findings. TSS was performed to remove the entire pituitary adenoma and to achieve an endocrinological cure at Toranomon Hospital in May 2004. (For this patient, postoperative hormonal replacement was not required.)

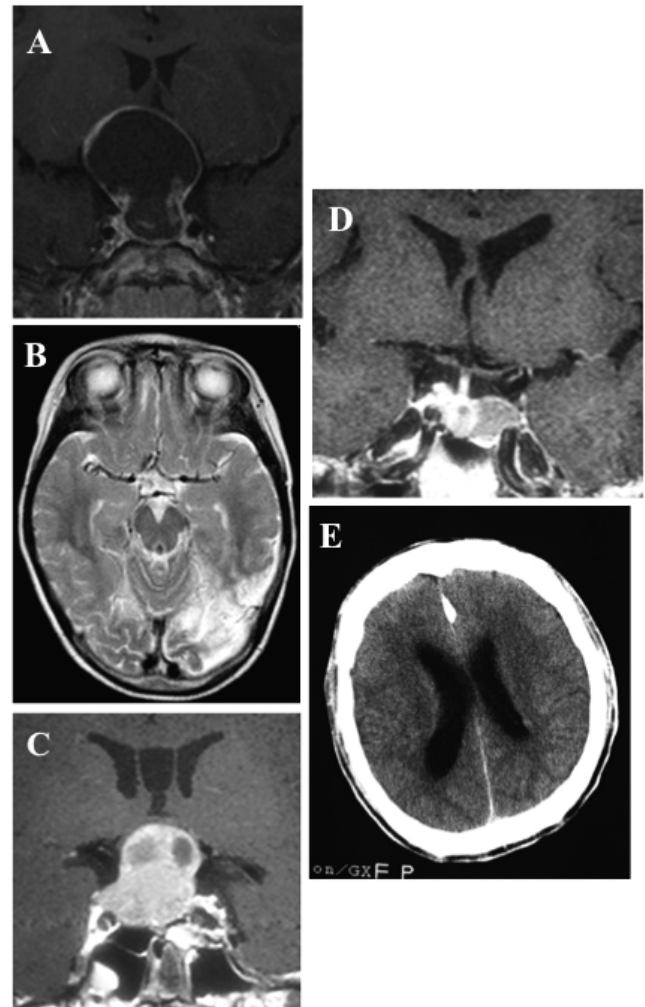


Fig. 1 A, B: A 4-year-old boy with craniopharyngioma. A: Preoperative MR imaging (Gd-enhanced T₁WI) reveal a large, cystic, dumbbell-shaped tumor. B: T₂WI revealed left occipital infarction due to postoperative SPM. C: A 40-year-old man with non-functioning adenoma. D, E: A 55-year-old man with acromegaly. D: Preoperative MR imaging E: CT revealed brain edema due to SPM. CT: computed tomography, MR: magnetic imaging, SPM: *Streptococcus pneumoniae* meningoencephalitis.

He received prophylactic antibiotics [sultamicillin tosilate hydrate (SBTPC)], was discharged 2 weeks after surgery without any evidence of infection, and immediately returned to his job.

However, 2 weeks later (4 weeks after TSS) he was transported to the nearest emergency hospital with consciousness disturbances, neck stiffness, and a high fever. He was diagnosed with SPM due to his clinical symptoms, CSF examination (cell counts: 28,864 μ L, protein: 612 mg/dl, glucose: 2 mg/dl), and CSF culture. He was treated intensively with appropriate antibiotics, but he suffered a temporal lobe infarction due to associated encephalitis. At present, this patient is partially disabled and requires assistance with his daily activities.

In this case, anaerobic Gram-positive rods and Gram-positive cocci had been found but *Str. pneumoniae* was not detected via intraoperative BCSM.

The clinical characteristics of these three cases are summarized in Table 1.

Discussion

I. Clinical characteristics and pathogenesis of SPM

Streptococcus species is known to cause meningoencephalitis in both children and adults, especially after

sinusitis, middle ear infections, and/or pneumonia by local extension or hematologic dissemination.^{5,6)} Reported intracranial or systemic complications of SPM include local complications, such as seizure, arterial occlusion, venous thrombosis, arterial vasculitis, arterial spasm, diffuse brain swelling, hydrocephalus, encephalitis, cranial nerve palsies, hearing loss, as well as systemic complications like septic shock, disseminated intravascular coagulation, acute renal failure, and adult respiratory distress syndrome.^{1,5-7)}

SPM has a rather high mortality rate (20% to 30%) despite recent developments of highly effective antibiotics.¹⁾ As in other reports,^{1,5,7)} SPM complications in our series were associated with very severe symptoms and a poor prognosis.^{1,5)} Neurological deficits due to arterial vasculitis or encephalitis remained in all three cases, one patient (Case 2) died due to severe associated brain edema. Similarly, cerebral infarctions in various areas found in our three cases suggest intracranial arterial occlusion due to arterial vasculitis associated with SPM.

To our knowledge, few SPM cases after surgery have been reported in other conditions, including a healthy immunocompetent man 3 months after a cochlear implant,⁸⁾ a 9-month-old girl with an underlying frontoethmoidal encephalomeningocele who received facial surgery,⁹⁾ and

Table 1 Summary of our three cases of post-TSS SPM

		Case 1	Case 2	Case 3
	Age/gender	4, M	40, M	55, M
	DM	(-)	(-)	(-)
	Surgical approach	Sublabial TSS	Transnasal TSS	Transnasal TSS
	Pathology of tumor	Craniopharyngioma	non-functioning adenoma	GH adenoma
CSF leakage	During surgery	(+)	(-)	(-)
	After surgery	(-)	(-)	(-)
	BCSM	Not exam	<i>Staphylococcus</i> species, <i>Klebsiella pneumoniae</i>	Gram-positive rods, anaerobic Gram-positive rods
	Perioperative antibiotics used	CEZ	CEZ	SBTPC
	Postoperative hormonal replacement	Hydrocortisone, levothyroxine sodium hydrate, DDAVP	(-)	(-)
SPM	Onset after surgery (week)	8 weeks	4 weeks	4 weeks
	Initial symptoms	High fever, headache and unconsciousness with generalized convulsion	High fever, severe headache with unconsciousness	Unconsciousness
CSF data	Cell counts	2530/ μ L	Not available	28864/ μ L
	Protein	134 mg/dl		612 mg/dl
	Glucose	12 mg/dl		2 mg/dl
	Outcome	SD	D	SD

BCSM: bacterial culture of sphenoidal sinus mucous membrane, CEZ: cefazoline sodium, CSF: cerebrospinal fluid, D: dead, DM: diabetes mellitus, GH: growth hormone, M: male, SBTPC: sultamicillin tosilate hydrate, SD: severely disabled, SPM: *Streptococcus pneumoniae* meningoencephalitis, TSS: transsphenoidal surgery.

a 5-year-old boy with obstructive sleep apnea who had undergone adenotonsillectomy.⁹⁾ Notably SPM after TSS has been reported in only one case in the literature.¹⁾ In this report Bakar and Hakki Tekkok¹⁾ described a 56-year-old man with SPM after TSS who became hyperpyrexia and progressed to confusion and lethargy 2 days after an uneventful surgery. Unlike our cases, these symptoms occurred early after surgery and the patient made an uneventful recovery, although CSF leakage was not observed throughout the course of meningitis as in our other cases. Indeed, postoperative meningitis after TSS is usually associated with postoperative CSF leakage early after surgery,^{2,3)} suggesting direct infection from the operative field to the intracranial region.

II. Inoculation routes of *Str. pneumoniae*

There have been no reports of similar types of SPM with a delayed onset in the absence of CSF rhinorrhea after any other intracranial surgery. However, there has been an increase in the number of reported cases of SPM in patients undergoing cochlear implants.¹⁰⁾ Like our cases, meningitis occurred more than 30 days after surgery in 20 of 29 children with SPM after cochlear implantation. Moreover, the inoculation routes of *Str. pneumoniae* in these cases were considered to occur via three different routes: hematogenously or directly through the middle or inner ear after cochlear implantation. Through experiments in rats, Wei et al.¹¹⁾ demonstrated that greater numbers of *Str. pneumoniae* were localized to postoperatively regenerated bony and fibrous tissue, and that persistence of the pathogens in these areas can reach the central nervous system via perineural and perivascular spaces that develop SPM after cochlear implantation. This finding is consistent with other studies showing a higher risk of late-onset pneumococcal meningitis after temporal bone fracture.¹²⁾

Therefore, it is plausible that the mechanism of late-onset SPM after TSS is similar to that of patients with cochlear implants or temporal bone fracture.^{11,12)} *Str. pneumoniae* might localize to postoperatively regenerated bony and fibrous tissue around the sellar floor after TSS, and late-onset meningoencephalitis may have occurred without CSF leakage by *Str. pneumoniae* infection, which then spread either hematogenously or directly to the central nervous system. Moreover, it is conceivable that reduced resistance to infection plays a role in the development of meningoencephalitis, and this might have been an associated factor in our three patients.

III. Clinical meaning of bacterial cultures of sphenoidal sinus

Small segments of sphenoid sinus mucous membranes obtained during surgery were cultured in 316 consecutive patients undergoing TSS or extended TSS for pituitary

tumors at Toranomon Hospital between January 2006 and July 2007. From these cultures, 31 various types of bacteria were detected. Moreover, bacterial cultures were positive in 276 (87.3%) patients and *Str. pneumoniae* was not found in any of the patients in this series. Postoperative meningitis occurred in only 2/316 patients (0.63%). In these two patients, nasal bacteria were not found in the culture of the sphenoidal sinus mucous membrane obtained during surgery. Similarly, *Str. pneumoniae* was not found in the culture of the sphenoidal sinus membrane in the two SPM patients that we examined, indicating that BCSM performed during surgery is useless for predicting postoperative meningitis after TSS or for the identification of responsible microorganisms.

IV. Prevention of postoperative SPM

Currently, our three cases with late-onset SPM after TSS confirmed that (1) SPM occurs suddenly in 1 or 2 months after an uneventful postoperative course without any pre-existing signs or symptoms and (2) SPM is not associated with CSF leakage. CEZ or SBTPC were administered as postoperative prophylaxis in our three SPM patients. Both CEZ and SBTPC are sensitive for *Str. pneumoniae* and have a wide spectrum. The first and second generations of cephem and beta-lactam antibiotics are recommended for the prevention of postoperative infections.¹³⁾ CEZ is the first generation of cephem and SBTPC is a beta-lactam antibiotic, and both are involved in these groups. Therefore, there appears to be no effective prophylaxis against delayed SPM after TSS. The most important lesson to be learned here is that every neurosurgeon dealing with pituitary lesions should know that this type of postoperative meningitis might occur, although it is extremely rare. In addition, we speculate that our three SPM patients had reduced resistance to infection, as the first case was a child, the second case was a man with moderate anemia because of two TSSs within a short span, and the third was a blue-collar worker who returned to his job immediately after discharge.

A *Str. pneumoniae* vaccine has recently been proven effective in preventing severe pneumonia and meningitis due to this organism.^{14,15)} Therefore, the preoperative use of a vaccine should be recommended for patients who will require TSS, especially in pediatric patients younger than 5 years, in patients older than 65 years, and in immunocompromised patients. Although there is no definitive evidence that this vaccine can prevent SPM following surgery, this should be taken into account given the seriousness of this condition and the poor prognosis of postoperative SPM.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, or devices in the article. All

authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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