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**Original Article**

# Microbiology and epidemiology of brain abscess and subdural empyema in a medical center: a 10-year experience

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**Background and purpose:** Brain abscess and subdural empyema are the 2 most common forms of intracranial pyogenic infections. Predisposing factors and etiological agents may change with time. This study examined the epidemiological features of these conditions.

**Methods:** The medical records of all inpatients with a diagnosis of brain abscess or subdural empyema from 1998 to 2007 were reviewed. The diagnosis was confirmed by imaging study or operative findings.

**Results:** 151 episodes of brain abscess were diagnosed in 150 patients, and 10 patients had subdural empyema. The incidence of brain abscess fluctuated over time, while that of subdural empyema remained stable. The mean ± standard deviation age of patients with brain abscess was significantly greater than that of patients with subdural empyema (48.5 ±19 years vs 25.4 ± 24 years; $p = 0.004$). The number of patients with hematogenous brain abscess increased from 7 in 1998 to 2002 to 19 in 2003 to 2007, while that of those with infection related to operation decreased from 10 to 5. Most subdural empyema was related to bacterial meningitis (4 of 10). Etiological agents were identified in 53% of brain abscesses, including *Enterobacteriaceae* spp. (21.3%), *Streptococcus* spp. (20%), and mixed pathogens (17.5%). *Klebsiella pneumoniae* was the most common enteric bacteria isolated (15.3%), especially in patients with diabetes mellitus, but was not observed in children younger than 18 years.

**Conclusions:** In contrast to western countries, *K. pneumoniae* plays an important role in intracranial pyogenic infections in Taiwan. The pathogens and routes of infection are different between children and adults.

**Key words:** Brain abscess; Empyema, subdural

## Introduction

Before the advent of imaging examinations and surgical techniques, intracranial pyogenic infection was a life-threatening condition. Brain abscess and subdural empyema are the 2 most common forms of these infections [1]. Brain abscess is a pus collection in the cerebrum and subdural empyema is infection in the space between the dura and arachnoid. The pathogenesis of both infections involves spread of a contiguous infection via the valveless diploic veins [2,3]. Therefore, they had long been considered a complication of otorhinologic or dental infections, accounting for as much as 50% to 80% of all cases [4,5]. However, these features may have changed because of aggressive antibiotic treatment for otorhinologic infections and increasing neurosurgical procedures [6]. As the causative pathogen is related to the original source of infection and the host immune status, a change in the microbiology of intracranial pyogenic infection may be expected if the dominant infection route has changed. To clarify whether epidemiological features of intracranial pyogenic infections have changed recently, this study analyzed the clinical characteristics,

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epidemiology, and microbiology of such infections in the past 10 years.

## Methods

The medical records of all patients with a diagnosis of brain abscess or subdural empyema (ICD-9-CM code 324.0) were reviewed from January 1, 1998 to December 31, 2007 at the National Taiwan University Hospital, a tertiary hospital in Taipei, Taiwan. Patients with only epidural abscess were excluded. The diagnosis of brain abscess was confirmed when computed tomography (CT) and/or magnetic resonance imaging (MRI) showed a localized parenchymal lesion with perilesional brain edema and postcontrast ring-enhancement. The radiologist's interpretation of the CT and MRI findings was accepted. Subdural empyema was defined as a fluid collection seen on CT and/or MRI with other relevant clinical findings.

The imaging findings were corroborated by pus aspiration, culture of the aspirate or pathological findings for the majority of patients. For patients who did not undergo surgical intervention, the diagnosis was reinforced by typical clinical symptoms and treatment response. If etiologies other than pyogenic infection could not be excluded confidently, the patient was excluded.

A distant hematogenous infection was defined as positive blood culture or clinically diagnosed culture-negative infective endocarditis or other obvious distant infection focus, such as necrotizing fasciitis. Pathogens isolated from blood culture in these patients or from the abscess, wound, drain, or cerebrospinal fluid were considered the causative agent of the brain abscess.

### Statistical analysis

For categorical variables, cross-table analysis was performed by using Fisher's exact test. Mann-Whitney *U* test was used to compare continuous variables. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 13.0; SPSS, Inc., Chicago, IL, USA). All *p* values were 2 sided.

## Results

### Demographics

151 episodes of brain abscess occurred in 150 patients, including 113 men and 37 women. The mean age was 48.5 years (median, 50 years; range, 0.5 months to 84 years). Eleven patients were younger than 18 years. In the pediatric population, the mean age was 7.6 years (range, 0.5 months to 18 years). Subdural empyema was diagnosed in 10 patients with a mean age of 25.4 years (median, 22.5 years; range, 2 months to 67 years). Four patients were younger than 18 years. The age of patients with subdural empyema was significantly younger than those with brain abscess ($p = 0.004$) [Fig. 1], while men outnumbered women for both conditions (the male-to-female ratio was 3 for brain abscess and 2.3 for subdural empyema). The incidence of brain abscess fluctuated in the past 10 years but that of subdural empyema remained stable (Fig. 2).

Fifty two percent of patients with brain abscess had at least 1 underlying disease. Potential risk factors differed between children and adults. In adult patients, diabetes mellitus was the most common risk factor (20%), followed by malignancy (17%), liver cirrhosis (9%), human immunodeficiency virus (HIV) infection (7%), heart disease (4%), pulmonary tuberculosis (3%), and end-stage renal disease (1%). Cyanotic congenital heart disease was the only underlying disease identified in pediatric patients (3/11). Only 2 patients with subdural empyema had underlying disease (diabetes mellitus and congenital heart disease). The percentage of patients with underlying diseases did not change significantly during the study period.

### Clinical presentation

The most common initial presentations of brain abscess were fever (57%), altered consciousness (55%), and headache (40%). Patients with contiguous infection were more likely to have headache (10/14 vs 51/137; $p = 0.006$). As for subdural empyema, altered consciousness was the most common symptom (70%), followed by fever (60%), nausea/vomiting (50%), and seizures (50%) [Table 1]. For the intracranial pyogenic infections, seizures were observed more frequently in patients younger than 18 years (7/14 vs 28/147; $p = 0.01$). Compared with adult patients, pediatric patients with brain abscess had lethargy more frequently as an initial presentation (55% vs 13%; $p = 0.002$).

### Source of infection

Forty two percent of patients with brain abscess (n = 64) had an identifiable infection source. Among them, 41% (n = 26) had a distant hematogenous focus, including 12 patients with infective endocarditis, 12 with bacteremia, and 2 with soft tissue infection.

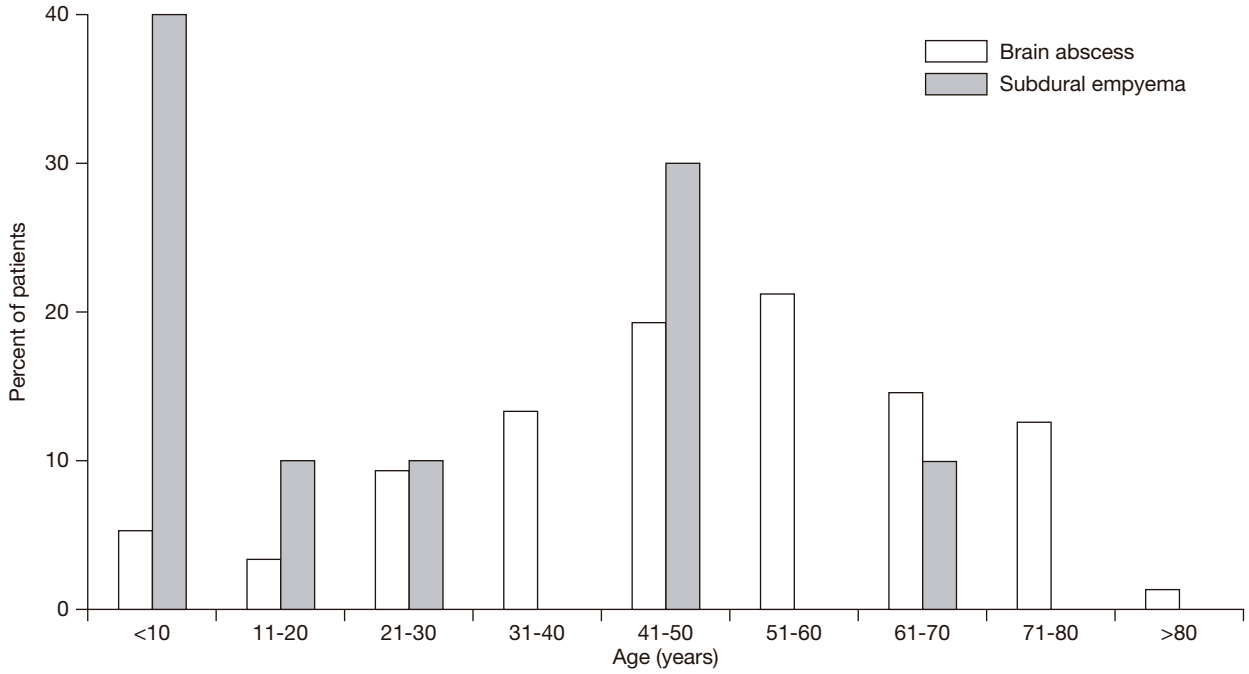


**Fig. 1.** Age distribution of patients with brain abscess and subdural empyema.

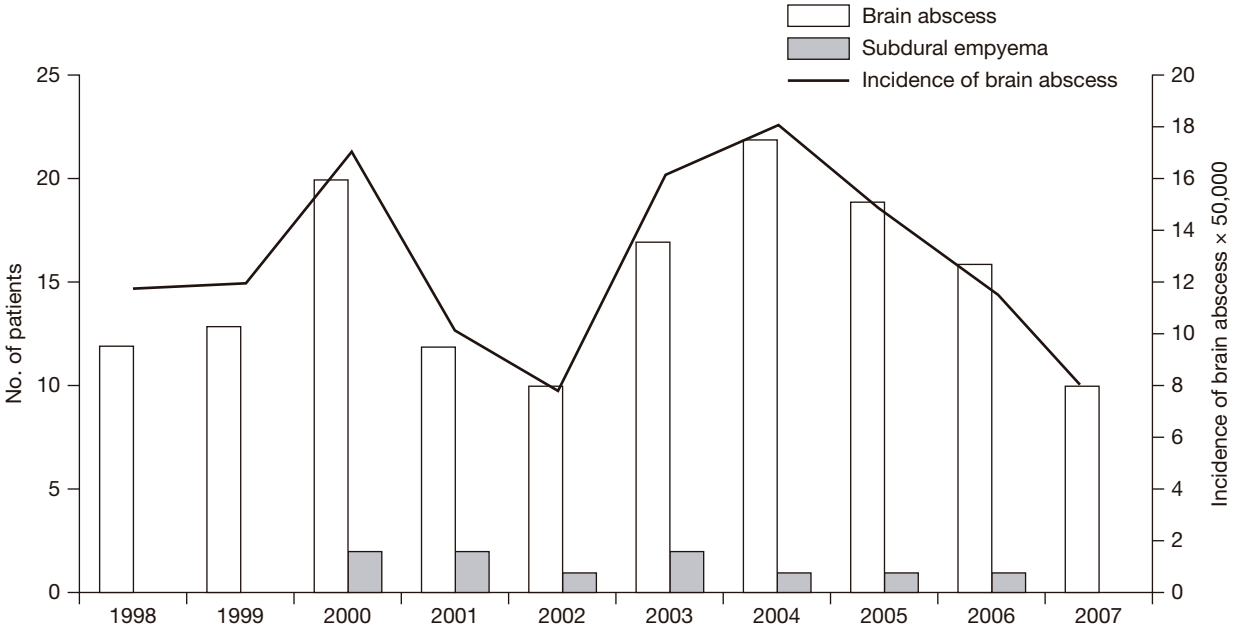


**Fig. 2.** Annual distribution and incidence[a] of patients with brain abscess and subdural empyema.
[a]Number of patients/total number of admissions in the corresponding year × 50,000.

Twenty three percent (n = 15) had operation-related infection and 22% (n = 14) had contiguous infection, including sinusitis (n = 8), mastoiditis (n = 5), and otitis media (n = 1). Another 14% of patients (n = 9) had meningitis-related infection. The number of patients with hematogenous brain abscess more than doubled from the period 1998 to 2002 (n = 7) to 2003 to 2007 (n = 19), while the number of patients with infection related to operation halved from 10 to 5 patients during the same period. The hematogenous route of spread occurred less frequently in the pediatric group than in the adult group (1/11 vs 25/140).

Seventy percent of patients with subdural empyema (n = 7) had an identifiable infection focus. All meningitis-related infection (n = 4; 57%) occurred between 2003 and 2007. Other infection routes

**Table 1.** Signs and symptoms of patients with brain abscess and subdural empyema.

| Variable | Brain abscess (n = 151) % | Subdural empyema (n = 10) % |
|---|---|---|
| Fever | 57 | 60 |
| Seizures | 20[a] | 50[b] |
| Headache | 40 | 30 |
| Nausea/vomiting | 19 | 50 |
| Altered consciousness | 55 | 70 |
| Focal neurological signs | 38[c] | 40[d] |
| Lethargy | 16 | 20 |
| Weakness | 24 | 10 |
| Meningismus | 16 | 10 |
| Bulging fontanelle | 0 | 30 |
| Increased deep tendon reflex | 5 | 20 |
| Positive Babinski sign | 7 | 20 |

[a]Eight patients had generalized seizures, 9 had focal seizures; the seizure pattern was not described for other patients.
[b]Two patients had focal seizures; details were not mentioned for the others.
[c]Including facial palsy (11%), hemiparesis (10%), ataxia (9%), ocular palsy (9%), dysarthria (7%), hemiplegia (6%), and dysphagia (5%).
[d]Including ocular palsy (30%) and dysarthria (10%).

included operation (n = 2) and otogenic infection (n = 1). The 3 pediatric patients had meningitis-related infection.

## Pathogens

Pathogens were identified in 80 of 151 episodes (53%) of brain abscess (Table 2). In order of etiologic importance, the predominant organisms causing brain abscess were *Enterobacteriaceae* (21.3%), *Streptococcus* spp. (20%), and mixed infection (17.5%). *Klebsiella pneumoniae* was the most common enteric bacteria isolated (15.3% of all isolates). Diabetes mellitus was present in 5 of 11 patients with *K. pneumoniae* infection. Other infection foci could be identified in 7 infections, including 3 disseminated infections (liver abscess with or without endophthalmitis), 2 meningitis, 1 necrotizing fasciitis, and 1 bacteremia. *Nocardia* spp. (2/10 vs 4/141) and *Cryptococcus* spp. (2/10 vs 0/141) were more commonly found in patients with HIV infection ($p = 0.004$). Anaerobes and mixed pathogens were more common in patients with unidentified infectious foci (6/64 patients with an identified focus vs 14/87 patients with no identified focus; $p < 0.01$). Half of the *Staphylococcus aureus* infections were associated with previous operation.

Compared with adults, *K. pneumoniae* was not isolated from children (0/11 vs 15/140), nor were Gram-positive bacilli (0/11 vs 12/140), *Cryptococcus* (0/11 vs 2/140), or *Mycobacterium avium* complex (0/11 vs 1/140) [Table 3]. This difference did not reach statistical significance.

In a comparison of the years 1998 to 2002 and 2003 to 2007, brain abscess caused by Gram-positive bacilli doubled from 4 to 8 and that by non–*S. aureus* Gram-positive cocci tripled from 5 to 15. The number of *S. aureus* isolates halved from 4 to 2 during the same period. The number of *K. pneumoniae* infections did not change significantly during recent years.

Eight of 10 patients with subdural empyema had pathogens identified. *Enterobacteriaceae* spp. accounted for 37.5%, including 2 *K. pneumoniae* and 1 *Escherichia coli*. Other isolates included *S. aureus* (n = 2), *Corynebacterium* spp. (n = 1), group B *Streptococcus* (n = 1), and *Haemophilus influenzae* type b (n = 1).

## Imaging study

The diagnosis of brain abscess was confirmed by MRI for 83 patients. The others were diagnosed by CT. Fifty two percent of all patients had a single brain abscess. Localized lesions, perifocal edema and mass effect were recorded in 144 (95%), 121 (80%), and 60 (40%) patients, respectively. Perifocal edema was more commonly seen by CT than MRI (60/68 vs 61/83; $p = 0.03$). Patients with a distant infection focus (17/26) or meningitis (8/9) tended to have multiple intracranial lesions compared with those with operation-related abscess (4/15) [$p = 0.01$].

The location of abscesses included cerebral hemisphere (80%), basal ganglia (14%), cerebellum (7%), midbrain (4%), thalamus (3%), and brain stem (2%). The most frequently involved lobe was the frontal lobe

**Table 2.** Pathogens isolated from patients with brain abscess.[a]

| Specimen | Pus | Blood | Cerebrospinal fluid | Other[b] | Total |
|---|---|---|---|---|---|
| Aerobes | | | | | |
| Gram-positive cocci | | | | | |
| *Streptococcus* spp. | 16 | 7 | 0 | 0 | 23 |
| *Staphylococcus* spp. | | | | | |
| Methicillin-sensitive *Staphylococcus aureus* | 2 | 1 | 0 | 0 | 3 |
| Methicillin-resistant *S. aureus* | 5 | 2 | 1 | 0 | 8 |
| Methicillin-resistant *Staphylococcus epidermidis* | 1 | 0 | 0 | 0 | 1 |
| *Gemella morbillorum* | 2 | 0 | 0 | 0 | 2 |
| *Enterococcus* spp. | 2 | 0 | 1 | 1 | 4 |
| Gram-positive bacilli | | | | | |
| *Nocardia* spp. | 3 | 1 | 0 | 2 | 6 |
| *Actinomyces* spp. | 2 | 0 | 0 | 0 | 2 |
| *Listeria* spp. | 0 | 2 | 1 | 0 | 3 |
| Unidentified | 0 | 1 | 0 | 0 | 1 |
| Gram-negative organisms | | | | | |
| *Enterobacteriacae* | | | | | |
| *Klebsiella pneumoniae* | 6 | 3 | 5 | 1 | 15 |
| *Enterobacter* spp. | 2 | 0 | 1 | 0 | 3 |
| *Escherichia* coli | 1 | 0 | 0 | 0 | 1 |
| *Serratia marcescens* | 1 | 1 | 0 | 1 | 3 |
| *Proteus mirabilis* | 0 | 1 | 0 | 1 | 2 |
| *Salmonella* spp. | 0 | 1 | 0 | 0 | 1 |
| Other | | | | | |
| *Pseudomonas aeruginosa* | 0 | 0 | 0 | 1 | 1 |
| *Morganella morganii* | 1 | 0 | 0 | 0 | 1 |
| *Haemophilus aphrophilus* | 1 | 0 | 0 | 0 | 1 |
| *Ralstonia picketti* | 0 | 1 | 0 | 0 | 1 |
| Anaerobes | | | | | |
| *Fusobacterium* spp. | 6 | 0 | 0 | 0 | 6 |
| *Eikenella corrodens* | 5 | 0 | 0 | 0 | 5 |
| *Peptostreptococcus* spp. | 4 | 0 | 0 | 0 | 4 |
| *Bacteroides* spp. | 3 | 0 | 0 | 0 | 3 |
| *Cryptococcus* spp. | 0 | 1 | 2 | 0 | 3 |
| *Mycobacterium avium* complex | 0 | 0 | 1 | 0 | 1 |

[a]Thirty five isolates were isolated from 14 patients with mixed infection.

[b]Other specimens included wound discharge, sputum, lung biopsy, and hemovac drain.

(54%), followed by the parietal (36%), temporal (27%), and occipital lobes (18%). Parietal and occipital lobe lesions were more commonly seen in the pediatric patients ($p = 0.05$ and $p = 0.03$, respectively). The lobe distribution did not relate to the route of infection.

One-half of patients with subdural empyema were diagnosed by CT and the other half by MRI.

## Cerebrospinal fluid examination

Cerebrospinal fluid (CSF) examination was performed for 50 of 151 episodes of brain abscess. The white blood cell (WBC) count ranged from 0 to 37,620/mm$^3$ (mean, 2085/mm$^3$). Pleocytosis (defined as WBC ≥10/mm$^3$) was noted in 33 episodes (66%), and 22 (44%) had pleocytosis of ≥100/mm$^3$. In patients with subdural empyema, 7 received CSF examination. The WBC count ranged from 0 to 540/mm$^3$. Five patients (71%) had pleocytosis ≥10/mm$^3$ and 4 (57%) had pleocytosis of ≥100/mm$^3$. Neutrophil predominance was a universal finding in patients with CSF pleocytosis. No complications related to lumbar puncture were recorded.

## Treatment and outcomes

Intravenous antibiotics were given to all patients. Third-generation cephalosporins (66%) with or without metronidazole were given to most patients with brain abscess. Vancomycin was used for 22% of

**Table 3.** Pathogens isolated from pediatric and adult patients with brain abscess.

| Pathogen | Pediatric patients (n = 11) No. | Adult patients (n = 140) No. |
|---|---|---|
| Aerobes | | |
| Gram-positive cocci | 4 | 50 |
| Gram-positive bacilli | 0 | 12 |
| Gram-negative organisms | 1 | 6 |
| Anaerobes | 1 | 19 |
| *Cryptococcus* spp. | 0 | 2 |
| *Mycobacterium avium* complex | 0 | 1 |

patients and penicillin was used for 13%. For subdural empyema, third-generation cephalosporins were used for 80% of patients. Metronidazole and vancomycin were each used for 40% of patients. For patients with brain abscess, 48% underwent at least 1 operation. Most operated lesions were single brain abscess ($p$ = 0.003). Owing to the tendency towards multiple lesions, patients with hematogenous infection and meningitis-related infection were less likely to undergo operation, compared with those who had operation-related or contiguous infection (5/26 and 1/9 vs 12/15 and 10/14, respectively; $p < 0.01$).

The overall mortality was 13% for brain abscess. Another 9% of patients were discharged with anticipated poor prognosis. Patients with underlying malignancy or liver disease had the poorest survival (12/23 and 2/6, respectively; $p = 0.002$). Initial consciousness disturbance was a poor prognostic factor ($p = 0.002$). Patients treated only medically had a poorer outcome (mortality, 27/78 vs 7/72; $p < 0.01$). Survival was not influenced significantly by age or infectious route.

All patients with subdural empyema survived. Surgical intervention was performed for 8 patients.

## Discussion

Compared with previous studies [6-9], this study presents a comprehensive review of intracranial pyogenic infections in Taiwan for both adults and children. Brain abscess and subdural empyema have a similar pathogenesis and the same male predominance. However, these conditions differ in their age distributions. Brain abscess is said to be predominant in patients in their 30s, while subdural empyema is a disease of adolescents [1]. This study showed a similar result. The peak age of patients with brain abscess (range, 40-70 years) appears to be older than that in other reports [1]. Fever was the most common clinical presentation of brain abscess. However, fever was present in only 55% of patients. Therefore, this diagnosis cannot be excluded in an afebrile patient.

According to the literature, the most common microbial source of brain abscess is a contiguous focus related to ear, sinus, or dental infections, which account for more than 50% of cases in most series [1,2]. Metastatic spread of a distant hematogenous infection (25%), trauma, or operation are other possible sources of brain abscess [1,2]. A change in the epidemiology had been expected since the 1990s, owing to a decreasing incidence of otogenic infections and an increasing number of immunocompromised patients [2,7]. In this 10-year review, brain abscess caused by a contiguous source and meningitis accounted for the minority of cases (20% and 15%, respectively). There was an abrupt increase in the number of cases caused by hematogenous infection from 27% in 1998 to 2002 to 50% in 2003 to 2007, while cases related to trauma or operation decreased from 38% in 1998 to 2002 to 13% in 2003 to 2007. There was no apparent change in the number of immunocompromised hosts. Interpretation of these findings may have some limitations. Firstly, all patients with a positive blood culture and without an obvious contiguous focus or operation history were considered to have a hematogenous source of infection. This may be an overestimate, since some studies suggest that blood cultures unreliably predict the complete microbiology of the abscess [8]. Only 1 patient in this series had 2 positive cultures, and the blood culture result of methicillin-resistant *S. aureus* correlated only partly with the pus culture result of methicillin-resistant *S. aureus* plus *K. pneumoniae*. Secondly, most anaerobic bacteria were isolated from patients with an unidentified infection route. As no patients had an obvious odontogenic focus, it is possible that a dental origin of infection was overlooked in some of these patients.

A contiguous focus, especially sinusitis, is considered to be the most common route of infection for subdural empyema, but meningitis has a more important role in causing pediatric subdural empyema than in causing brain abscess [1,3]. One-half of infections (n = 4) in 2003 to 2007 were meningitis-related and 3 of the patients were younger than 1 year at diagnosis. Therefore, as the management of sinusitis improves, subdural empyema is no longer a disease in teenagers with frontal sinusitis [1,5], but rather a disease of previously healthy infants with meningitis.

The causative pathogens of intracranial pyogenic infections vary with the mode of infection, age, and underlying condition of the patients. The mode of infection is considered to be the most important determinant [6]. The most common etiologic agents for brain abscess in other reports are *Streptococcus* spp., anaerobic bacteria, *S. aureus*, and *Enterobacteriaceae*. The percent of cases caused by *Streptococcus* spp. was as high as 74% in earlier reports [9], but has decreased to 8% to 22% in recent studies [6,7,10]. This study showed that brain abscesses caused by *S. aureus* decreased markedly during the study period. As *S. aureus* is commonly associated with surgical wound infection, this decrease in *S. aureus* infection may be secondary to the decrease in operation-related infections.

It is noteworthy that all studies performed in Taiwan, including this study, indicate that *K. pneumoniae* is an important cause of brain abscess, accounting for 7% to 20% of all cases [6,11,12]. *K. pneumoniae* has been known to cause a distinct bacteremic syndrome and meningitis in Taiwan since the 1990s [13]. It has been reported that genotype K1 plays an important role in central nervous system complications following bacteremia and liver abscess in Taiwan [14]. If an invasive genotype is the major cause of disseminated infections, the infection may be expected to occur both in adults and children. However, *K. pneumoniae* has not been isolated in patients younger than 18 years. This finding is concordant with another review of 53 patients in Taiwan, in which *K. pneumoniae* was noted in 7% of all isolates, but none of them came from children younger than 18 years [11]. The reason for the geographic preponderance and the age predilection of severe *K. pneumoniae* infection is still unknown. In addition to the virulence factor of different bacterial strains, some host factors may contribute to this unique feature of *K. pneumoniae* infection in Taiwan [13]. As severe *K. pneumoniae* infection tends to occur in patients with diabetes mellitus, as suggested by this study and another report [11], this may be the reason why it is relatively rare in children.

Pathogens of subdural empyema may provide a good indication of infection routes. In contrast to previous reports suggesting that *Streptococcus milleri* and other *Streptococcus* spp. are the most common pathogens [3], pathogens isolated in this study and the study by Wu et al [15] were those more commonly associated with bacterial meningitis. The decreased incidence of sinusitis-related subdural empyema and the increased incidence of meningitis-related subdural empyema may explain this change in bacteriology.

MRI and CT scan are both helpful for diagnosing brain abscess [1]. The number and location of lesions are usually related to the infection route [16]. For example, frontal and temporal lesions are usually related to a contiguous focus. More than half of the patients in this study had multiple lesions, most of which may have arisen from hematogenous spread of pathogens so the origin of infection may be hard to determine.

CSF examination was not suggested for patients with suspected brain abscess because of its low specificity for diagnosis, normal findings, and potential risk for brain herniation [1,2,17]. With an initial suspicion of meningitis, one-third of the patients underwent CSF examination, and pleocytosis was detected in 66%. Meningitis is believed to be a rare cause of brain abscess except for in newborns and children [1].

The mortality rate for brain abscess in this series was compatible with that of other reports in the post-CT era [10,18]. This study showed that the most important predictive factors for mortality are initial consciousness level and underlying condition, which is concordant with previous reports [18,19]. Other prognostic factors mentioned in other reports, including infection focus, did not correlate significantly with survival in this series [10,19]. The effect of operation on mortality may have a selection bias [18]. Consistent with other reports, the survival rate for subdural empyema has improved dramatically in the past 10 years [15].

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