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Klebsiella meningitis in Taiwan: an overview

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SUMMARY

Klebsiella infection has been considered to be an uncommon cause of meningitis. To determine its incidence and clinical features, we reviewed the microbiologic records of cerebrospinal fluid (CSF) and blood cultures and the medical records of patients with bacterial meningitis admitted between 1981 and 1995. Klebsiella meningitis was diagnosed in 79 patients with 83 episodes. All patients had klebsiella isolated from CSF and/or blood and typical symptoms and signs of acute bacterial meningitis. Of these, 74 were over 16 years of age and 2 of the 5 children were infants. There was an increased prevalence rate of klebsiella meningitis after 1986. Of the 83 episodes, only 9 occurred between 1981 and 1986, accounting for 7·8% of 115 cases with CSF and/or blood culture-proven acute bacterial meningitis, whereas in 1987–95, there were 74 episodes accounting for 17·7% of 419 bacteriologically proven cases. *K. pneumoniae* accounted for 69 episodes, *K. oxytoca*, 11 episodes and *K. ozaenae*, 3 episodes. Male gender, diabetes mellitus and liver cirrhosis were commonly associated with *K. pneumoniae* meningitis. Neurosurgical procedures were frequently associated with *K. oxytoca* meningitis. All three patients with *K. ozaenae* meningitis had a primary disease of the nasopharyngeal pathway. The mortality rate due to *K. pneumoniae* was 48·5%, *K. oxytoca*, 10% and *K. ozaenae*, 0%. In patients with *K. pneumoniae* meningitis, poor prognostic factors included age over 60 years, diabetes mellitus, bacteremia and severe neurological deficits on the first day of treatment.

INTRODUCTION

Bacterial meningitis remains a major cause of death and long-term neurologic sequelae worldwide. The specific microorganisms responsible for bacterial meningitis vary with time, geography and patient age. Meningitis caused by klebsiella has been rare. In the United States, only 7 cases of klebsiella meningitis were found in a review of 3377 cases of meningitis diagnosed between 1917 and 1947 [1]. A second study showed that klebsiella comprised only 1·5% of all cases of meningitis seen at one institution between 1936 and 1956 [2].

Klebsiella accounted for 1 of 86 adult cases of bacterial meningitis between 1970 and 1982 [3]. In a study from Germany, none of the bacterial meningitis in 86 adult patients was caused by klebsiella [4]. In a recent study from the United States, 16 (4·5%) of 354 single episodes of culture-proven adult meningitis were due to klebsiella [5]. In both Singapore [6] and Taiwan [7, 8], there has been an increased incidence of klebsiella meningitis in adults.

We have recently published investigations of patients with meningitis caused by three species of *Klebsiella*: *K. pneumoniae* [8], *K. oxytoca* [9] and *K. ozaenae* [10]. Because klebsiella has become an

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increasingly common causative pathogen of bacterial meningitis in Taiwan, we reviewed all cases of bacterial meningitis diagnosed during a 15-year period, focusing on the secular trends, clinical and laboratory findings, and prognostic factors associated with poor outcome between infections caused by *Klebsiella* sp. and other bacterial causes of meningitis.

PATIENTS AND METHODS

We reviewed the microbiologic records of cerebrospinal fluid (CSF) and blood cultures and the medical records of patients with bacterial meningitis admitted between 1981 and 1995. All patients were treated at Chang Gung Memorial Hospital, a 3500-bed acute-care teaching hospital located in the northern part of Taiwan which serves as a tertiary case centre for the entire country. The criteria for inclusion in the study included either (i) demonstration of klebsiella in CSF culture, history of acute disease and presence of clinical features of meningeal inflammation, or (ii) demonstration of klebsiella in blood culture; history of acute disease with clinical findings such as headache, fever and nuchal rigidity; and typical CSF features of decreased glucose level, increased protein concentration and pleocytosis with predominant polymorphonuclear cells. The criteria used for the diagnosis of bacterial meningitis due to other pathogens were the same as those used for klebsiella meningitis.

We recorded data on age, sex, clinical manifestations of the illness, associated diseases, head injury or neurosurgical procedure, laboratory findings, antibiotic therapy and outcome. Clinical severity on the first day of antibiotic therapy was classified into two stages: Stage I: patients with mildly or non-altered consciousness and/or focal neurological signs such as hemiparesis; and Stage II: patients in a state of delirium or coma. Meningitis was defined as either nosocomial or community-acquired [11]. Initial antibiotic therapy was considered appropriate when the antibiotic administered on the day of diagnosis was demonstrated to be effective against the pathogen by sensitivity testing and the antibiotic used was capable of reaching the central nervous system (CNS) in adequate concentrations.

We examined the secular trend of klebsiella meningitis in respect to the total number of culture-proven bacterial meningitis cases. Seasonal variation of meningitis caused by *K. pneuominae* was analysed.

Table 1. *Causative organisms of bacterial meningitis, Taipei, Taiwan, 1981–95*

Organism	*n*	%
Gram-negative bacilli		
Non-klebsiella species	145	27·2
Klebsiella species	74	13·8
Streptococcus species	156	29·2
Staphylococcus species	64	12·0
Haemophilus influenzae	55	10·2
Neisseria meningitidis	10	1·9
Listeria monocytogenes	7	1·3
Bacillus species	4	0·8
Corynebacterium species	1	0·2
Mixed bacterial species*	18	3·4
Total	534	100·0

* Nine episodes were caused by klebsiella and another microorganism.

The clinical presentations and outcomes were discussed for each type of klebsiella meningitis.

Data analysis

All statistical analyses were performed on an IBM-PC compatible computer, using the Stata software package [12]. Comparison between groups was made by means of the unpaired Student's t test for normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, and the Pearson χ^2 or Fisher exact test for nominal variables. All P-values were two-sided. The level of significance was 0·05.

Univariable analysis was calculated by means of Pearson χ^2 test. Variables selected from univariate analyses were sequentially deleted from a full model of multivariate logistic regression until no remaining candidate variable met the significance level of 0·2. Interaction was initially assessed in the stratification analysis with the Mantel–Haenszel test for heterogeneity, and then examined in the final model. The analysis was done only on adults aged over 15 years since all but four episodes of *K. pneumoniae* meningitis occurred in adults. All the comparisons were based on episodes of meningitis instead of patients, unless otherwise specified.

RESULTS

Bacterial microorganisms were demonstrated in the CSF and/or blood in 534 episodes of bacterial meningitis (Table 1). Of the 534 episodes, 83 were

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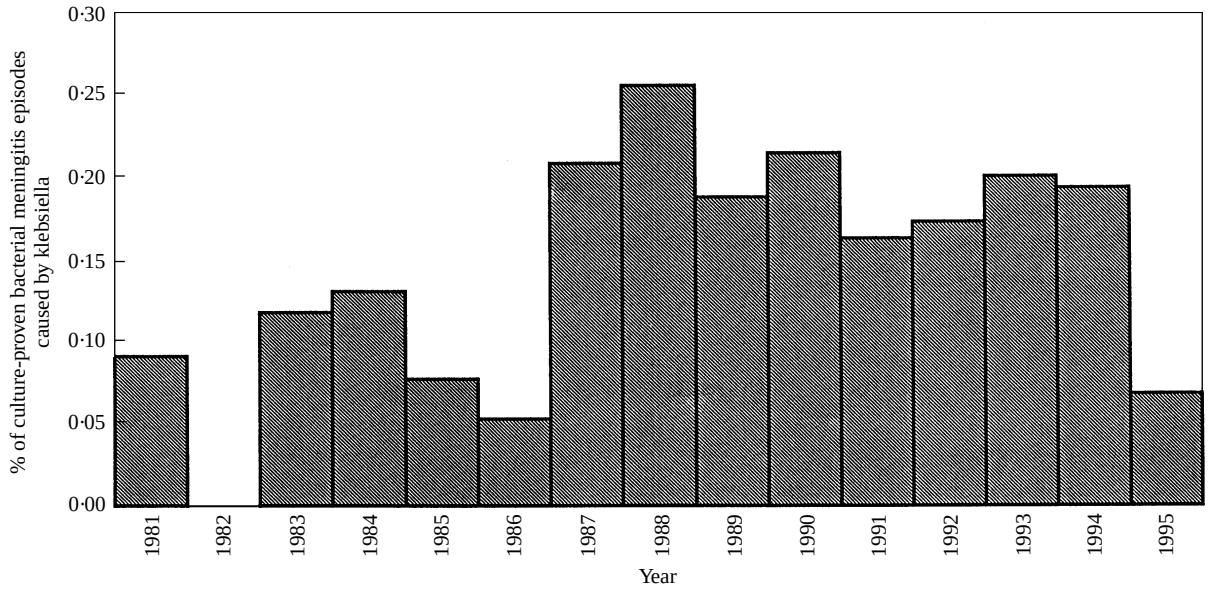

Fig. 1. Proportion of culture-proven bacterial meningitis episodes caused by Klebsiella species, Taipei, Taiwan, 1981–95.

caused by klebsiella in 79 patients. There were 55 (70%) men and 24 (30%) women, aged between 15 days and 82 years. Of these, 74 were over 16 years of age (mean, 46·8 ± 16·0 years). Two of the five children were infants. *K. pneumoniae* accounted for 69 episodes of meningitis, *K. oxytoca*, 11 episodes and *K. ozaenae*, 3 episodes. Four of the 79 patients had 2 episodes of infection; 3 were caused by *K. pneumoniae* and 1 by *K. oxytoca*.

There was a higher prevalence rate of *klebsiella* meningitis in respect to the total number of culture-proven bacterial meningitis cases after 1986 (Fig. 1). Of the 83 episodes, only 9 occurred between 1981 and 1986, accounting for 7·8% of 115 cases with CSF and/or blood culture-proven acute bacterial meningitis. In the following years (1987–95), there were 74 episodes, 17·7% of 419 bacteriologically proven cases.

Klebsiella pneumoniae meningitis

There were 66 patients with 69 episodes of *K. pneumoniae* meningitis. The male:female ratio was 3·1:1 (50 men and 16 women). Of these, 62 were over 16 years of age (mean, 45·9 ± 16·7 years). Of the 69 episodes, 36 were primary meningitis and 33 were secondary to trauma and/or neurosurgical procedures. The infection was nosocomial in 14 episodes and community acquired in 55. Of the 14 nosocomial episodes, 13 (93%) occurred in neurosurgical and/or head injury patients. Seasonal variation was not noted; the relative frequencies of *K. pneumoniae* meningitis for all bacteriologically proven cases were 13% from March to May, 16% from June to August, 13% from September to November, and 10% from December to February (P-value = 0·447, goodness-of-fit χ^2 test).

One underlying disease or condition was present in 52% of patients and more than one in 39%. Head injury, neurosurgical procedure, diabetes mellitus (DM), CSF leakage and alcoholism were most common. Liver cirrhosis was present in six patients and liver abscess in three. Male gender, DM, alcoholism, and liver cirrhosis were conditions more common in patients with *K. pneumoniae* meningitis than in patients with non-klebsiella bacterial meningitis (Table 2).

On the day of admission or diagnosis, all patients had a history of headaches, fever and/or neck stiffness. Disturbance of consciousness was noted initially in 66·7% of patients and seizure in 14·5%. A CSF study was performed on every patient (Table 3). A difference was observed in the median values of WBC count, protein and lactate between *K. pneumoniae* meningitis and other bacteriologically proven meningitis; however, there was a large overlap. All *K. pneumoniae* isolates were susceptible to third-generation cephalosporins and all but 10 to chloramphenicol.

Initial antibiotic therapy was appropriate in 61 episodes. Of the 45 patients treated with cefotaxime, moxalactam, ceftriaxone or ceftazidime, 24 survived and 21 died. Of the 16 patients treated with chloramphenicol alone or in combination with gentamicin,

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Table 2. *Common associated factors for* K. pneumoniae *meningitis in adults, Taipei, Taiwan, 1981–95*

Variable	Univariate analysis			Multivariate analysis	
	K. pneumoniae meningitis	Non-klebsiella meningitis	*P*	OR	95% CI
No. of episodes	65	248			
Age ⩾ 60	13 (20·0)	63 (25·4)	0·366		
Male	52 (80·0)	155 (62·5)	0·008	2·42	1·14–5·17†
Diabetes mellitus	18 (27·7)	18 (7·3)	< 0·001	8·24	3·33–20·43‡
Alcoholism	10 (15·4)	9 (3·6)	< 0·001	2·24	0·72–7·03
Liver cirrhosis	6 (9·2)	3 (1·2)	0·001	7·82	1·59–38·56†
Nosocomial infection	14 (21·5)	93 (37·5)	0·016	.	…
CSF leakage	9 (13·9)	23 (9·3)	0·279	2·40	1·00–5·89
n.s. and/or head injury	31 (47·7)	136 (54·8)	0·304	.	…

Percentages are given in parentheses.
n.s., neurosurgical procedures.
* Adjusted for gender and age.
† $P < 0·05$.
‡ $P < 0·001$.

Table 3. *WBC count, glucose, protein, and lactate in cerebrospinal fluid of patients with* K. pneumoniae *and non-klebsiella bacterial meningitis, Taipei, Taiwan, 1981–95*

Bacterial meningitis	WBC ($\times 10^6$/l)	Glucose (mmol/l)	Protein (g/l)	Lactate (mmol/l)
K. pneumoniae				
Median	1927*	0·42	4·4*	16·4*
range	11 ~ 79500	0·1 ~ 12·9	0·1 ~ 23·0	2·1 ~ 33·3
n	58	59	55	47
Non-klebsiella				
Median	630	0·97	1·88	9·2
range	2 ~ 72400	0·1 ~ 9·4	0·1 ~ 50·0	1·8 ~ 37·2
n	355	362	335	259

* $P < 0·05$, comparing between *K. pneumoniae* and non-klebsiella bacterial meningitis, two-sample Wilcoxon rank-sum test.

9 survived and 7 died. Eights patients had inappropriate initial therapy and four died despite subsequent use of appropriate therapy.

Of the 66 patients, 32 (48·5%) died. A higher mortality was observed in the elderly (Table 4); the mean age of the fatal group with 32 episodes of meningitis was 52 ± 16 years and the mean age of the non-fatal group with 37 episodes was 35 ± 18 years ($P = 0·0001$, *t*-test). Predictors of outcome also included DM ($P < 0·05$), bacteremia ($P < 0·05$) and clinical status on the first day of treatment ($P < 0·001$). The mortality rate was not significantly different between patients with community acquired meningitis and patients with nosocomial meningitis (case fatality rates, 25/55 vs. 7/14, $P > 0·05$, Fisher's exact test).

Multivariate analysis: Common associated factors for *Klebsiella pneumoniae* (Table 2)

In univariate analysis, male, DM, alcoholism and liver cirrhosis were significantly more frequent in patients with *K. pneumoniae* meningitis. Nosocomial bacterial meningitis was more likely to be caused by non-klebsiella bacteria.

With multivariate logistic modelling, adjusted for age and gender, DM and liver cirrhosis remained

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Table 4. *Predictors of mortality of* K. pneumoniae *meningitis in 69 episodes, Taipei, Taiwan, 1981–1995*

Variable	Fatal cases (%)	*P*
Age (year)		0·014
< 60	22/56 (39·3)	
⩾ 60	10/13 (76·9)	
Gender		0·417
Male	26/53 (49·1)	
Female	6/16 (37·5)	
Diabetes mellitus		0·045
Yes	12/18 (66·7)	
No	20/51 (39·2)	
Head injury and/or neurosurgical procedure		0·010
Yes	10/33 (30·3)	
No	22/36 (61·1)	
Alcoholism		0·105
Yes	7/10 (70·0)	
No	25/59 (42·4)	
Liver cirrhosis		0·852
Yes	3/6 (50·0)	
No	29/63 (46·0)	
Seizure		0·662
Yes	4/10 (40·0)	
No	28/59 (47·5)	
Bacteremia		0·019
Yes	22/37 (59·5)	
No	20/32 (31·3)	
Source of infection		0·761
Community	25/55 (45·5)	
Nosocomial	7/14 (50·0)	
Malignancy		0·117
Yes	4/5 (80·0)	
No	28/64 (43·8)	
CSF WBC count ($\times 10^6$/L)		0·684
⩽ 5000	18/37 (48·7)	
> 5000	14/32 (43·8)	
CSF sugar level (mmol/L)		0·807
< 2·5	23/46 (50·0)	
⩾ 2·5	6/13 (46·2)	
Stage		< 0·001
I	1/16 (6·3)	
II	31/53 (58·5)	

significant. The effects of both were large (odds ratios, 8·24 and 7·82, respectively). However, the 95% confidence interval for liver cirrhosis was wide because the number of patients with the condition was relatively small. The significance of CSF leakage was marginal. Since alcoholism was multivariably correlated with gender, liver cirrhosis and DM, it was insignificant in the final model. Neurosurgical conditions and the source of infection were no longer significant in the multivariate modelling procedure.

Klebsiella oxytoca meningitis

Nine of the 10 patients (3 men and 7 women) with 11 episodes were adult (mean age, 51·3 ± 10·1 year). Seven episodes were nosocomial and four community acquired. Four were mixed bacterial meningitis. All patients but one had undergone neurosurgical procedures. Three patients had DM. The most common presenting symptoms and signs were headache (72%), fever (72%), neck stiffness (72%) and disturbance of consciousness (63%). All patients had pleocytosis with predominant polymorphonuclear cells in the CSF studies. The CSF cultures for *K. oxytoca* were positive in all episodes and the blood cultures, positive only in two episodes. All *K. oxytoca* isolates were susceptible to third-generation cephalosporins and all but one to chloramphenicol. Antibiotic therapy was successful in nine patients, but failed in one who had been treated with cefotaxime.

Klebsiella ozaenae meningitis

There were three patients with *K. ozaenae* meningitis (Table 5) of whom two had been previously reported [10]. We encountered the third case in 1994. All three patients were over 50 years old. They all had a primary disease of the nasopharyngeal pathway: one had an intracranial extension of nasopharyngeal carcinoma, one had surgery for ozena, and the third had nasal polyps plus CSF leakage after a head injury. The patients recovered after antibiotic therapy with either chloramphenicol or third-generation cephalosporins.

DISCUSSION

The genus *Klebsiella* is usually found in the gastrointestinal tracts of humans and animals. This micro-organism occurs in faeces, soils, water, grain, fruits and vegetables. In man, it accounts for a significant proportion of urinary tract, blood stream, lung and surgical wound infections. In Taiwan, klebsiella infection of the liver [13, 14], the lungs [15] and the CNS [7, 8] is relatively common. Three species of *Klebsiella*, *K. pneumoniae*, *K. oxytoca* and *K. ozaenae* are known to cause meningitis.

Klebsiella pneumoniae meningitis

Of the three species, *K. pneumoniae* is the most common one to cause human infection. In Taiwan, it is a major cause of bacteremia [16], pyogenic liver

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Table 5. *Features of* Klebsiella ozaenae *meningitis from the English language literature and Taipei, Taiwan*

[Reference]	Age	Sex	Associated condition	Source of positive culture	Antibiotics used	Outcome
[32]	62	M	Pneumonia, hyperglycemia	CSF, blood	Penicillin, chloramphenicol, gentamicin	Death
[33]	78	F	Diabetes mellitus, sinusitis, otitis media	CSF, middle ear, maxillary sinus	Cefotaxime	Recovery
[17]	55	M	Nasopharyngeal carcinoma	CSF, blood	Penicillin, moxalactam	Recovery
[17]	53	F	Atrophic rhinitis, turbinectomy, ethmoidectomy	CSF	Penicillin, chloramphenicol, gentamicin	Recovery
Present report	58	M	Nasal polyps, CSF leakage after a head injury	CSF, blood	Cefotaxime	Recovery

abscess [13, 14], bacteremic pneumonia [15] and Gram-negative bacillary meningitis [7]. There has been an increased rate of *K. pneumoniae* meningitis in recent years. The reason is not clear, but studies from both northern and southern parts of Taiwan have demonstrated an increased rate of the disease [7, 8, 17]. In our hospital, the increase in absolute numbers of cases during the last 9 years of study may be partly due to the increased number of patient beds. There has been no change in the diagnostic techniques for the disease or change in the referral practice of patients sent to us. Seasonal trends for pathogens do appear [18, 19]. In the northern United States, *Haemophilus influenzae* meningitis is more prevalent in Autumn and Spring whereas *Neisseria meningitidis* occurs more commonly in Winter. A distinct seasonality was not noted in our patients although slightly more cases of *K. pneumoniae* meningitis occurred in the Summer.

Slightly increased rates of all types of bacterial meningitis have been shown in males compared with females [20]; this predisposition occurred also in our patients with non-klebsiella bacterial meningitis. In our study, susceptibility of males to *K. pneumoniae* meningitis seems excessively high; males outnumbered females by a ratio of 3:1. *K. pneumoniae* meningitis was commonly seen in infants in India [21], Nigeria [22], Spain [23], the United States [2, 24], and Thailand [25], but not in our study from Taiwan; there were only 2 infants in our 66 patients with this infection. The higher incidence of the infection in adults has also been observed by others in the United States [26] and in Singapore [6]. Mortality is also age-related; of our 13 patients over 60 years of age, 10 died.

K. pneumoniae has become an important cause not only in community-acquired meningitis, but also in nosocomial meningitis. In this study, 13 (93%) of the 14 episodes of nosocomial meningitis were found in neurosurgical and head injury patients. This is consistent with the previous study which demonstrated that klebsiella is the most common pathogen isolated from neurosurgical patients with meningitis [27].

In Taiwan, the frequencies of DM in patients with *K. pneumoniae* liver abscess [14] and in patients with *K. pneumoniae* bacteremia [16] are significantly high. In the present study, DM was more commonly seen as an underlying condition for patients with *K. pneumoniae* meningitis than for patients with non-klebsiella bacterial meningitis (27·7% *vs.* 7·3%, $P < 0{\cdot}001$). Previous studies have shown that the incidence of DM in patients with *K. pneumoniae* meningitis is higher than in the general population [28, 29]. Also, diabetic patients were associated with an increased mortality (66·7% *vs.* 39·2%, $P < 0{\cdot}05$).

Alcoholism was a poor prognostic factor for patients with klebsiella bacteremic pneumonia; all 11 alcoholic patients with the infection died despite adequate antibiotic therapy [15]. In our study, alcoholism appeared to be strongly associated with *K. pneumoniae* meningitis. Although it was insignificant in the multivariate analysis; this can be explained by the co-occurrence of the condition with other factors such as gender, DM, and liver cirrhosis. The mortality trend was higher in patients with alcoholism than in those without (70% *vs.* 42%), although the difference was not significant ($P > 0{\cdot}05$).

It was not surprising that patients with *K. pneumoniae* meningitis might be associated with a concomitant liver abscess, since the pathogen has been the leading causative microorganism in pyogenic liver abscess in Taiwan [13, 14]. The hepatobiliary tract likely acts as a portal of entry for the bacteria to cause pyogenic abscesses in diabetic patients [13, 16].

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However, it may not be significant in patients with *K. pneumoniae* meningitis because in our 66 patients with 69 episodes of meningitis, only 3 also had a liver abscess. In a Taiwan study of *K. pneumoniae* bacteremia, liver cirrhosis was present in 8 of 98 patients [16]. In our patients with *K. pneumoniae* meningitis, it was a common associated factor; 6 (9·6%) of 62 adult patients with the infection also had underlying cirrhosis. However, liver cirrhosis was not an outcome predictor of klebsiella meningitis.

The clinical status at the beginning of treatment has an important prognostic implication. The mortality rate of patients in stage I was significantly lower than that of patients in stage II (case fatality rates, 1/16 *vs.* 31/53, $P < 0{\cdot}001$). The overall mortality rate of *K. pneumoniae* meningitis has been high. In the Singapore study, all 20 patients with the infection died [6]. In two studies from the United States, the mortality rates of patients were 38% and 91%, respectively [26, 27]. In our present study, the mortality rate remained high (48·5%) despite our frequent use of third-generation cephalosporins in recent years.

Klebsiella oxytoca meningitis

K. oxytoca, biochemically similar to *K. pneumoniae* but indole sensitive, produces infections similar to those caused by *K. pneumoniae*. However, *K. oxytoca* meningitis is a rare disease which has been recognized only in recent years. The microorganism had not been isolated from any CNS infection at our institution until 1989 [9]. Up to 1995, 10 patients with 11 episodes of *K. oxytoca* meningitis were diagnosed. These accounted for 3·2% of 348 episodes with blood and/or CSF culture-proven bacterial meningitis between 1989 and 1995.

In general, the clinical features and the CSF findings in *K. oxytoca* meningitis were not qualitatively different from those in *K. pneumoniae* meningitis. In our patients with *K. oxytoca* meningitis, neurosurgical procedures, but not DM, were frequently associated. These procedures offer the direct means for *K. oxytoca* to reach the meninges and to cause meningitis. Two patients treated with chloramphenicol and 8 of 9 patients treated with third-generation cephalosporins recovered from the infection.

Klebsiella ozaenae meningitis

K. ozaenae is a biochemically inactive strain of *K. pneumoniae*. The microorganism is the same genospecies of *K. pneumoniae*, but is considered a separate strain because of its association with specific human disease. It is recognized as a cause of chronic inflammatory disease of the upper respiratory tract – ozena, a progressive fetid atrophy of the nasal mucosa found primarily in the tropics. *K. ozaenae* has been isolated from blood, wound abscess, sputum and the external auditory meatus of humans without clinical features of ozena [30]. It has also been implicated as a cause of infection of the urinary tract, soft tissue, middle ear and blood [31].

Meningitis caused by *K. ozaenae* is rare. The clinical features and the CSF findings of *K. ozaenae* meningitis are not qualitatively different from those of *K. pneumoniae* meningitis. The microorganism, a colonizer of the oro- and naso-pharyngeal mucosa, may reach the CNS by contiguous spread from the cranial structures. Of the three patients from Taiwan, all had a unique feature of primary disease of the nasal pathway. *K. ozaenae* may also enter the CNS by the hematogenous route. Of the two patients reported from the United States, pneumonia and hyperglycemia were noted in one [32] and otitis media, sinusitis and DM in the other [33]. One patient treated with third-generation cephalosporins recovered whereas the other one treated with chloramphenicol died.

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