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Comparison of the clinical characteristics and outcomes of *Klebsiella pneumoniae* and *Streptococcus pneumoniae* meningitis

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ABSTRACT

This multicenter, retrospective cohort study compared the clinical characteristics and outcomes of community-acquired *Klebsiella pneumoniae* meningitis (CA-KPM) with those of community-acquired *Streptococcus pneumoniae* meningitis (CA-SPM). Eighty-three adult patients, 27 with CA-KPM and 56 with CA-SPM, were included. Diabetes mellitus (48.1% versus 21.4%; $P = 0.01$) and liver cirrhosis (22.2% versus 5.4%; $P = 0.05$) were more commonly associated with CA-KPM. Comatose mental status (40.7% versus 12.5%; $P = 0.01$), septic shock (44.4% versus 8.9%; $P < 0.001$), and concomitant extrameningeal infections (40.7% versus 7.1%; $P = 0.001$) were also more common in the CA-KPM group. The 28-day mortality (44.4% versus 10.7%; $P < 0.001$) and inhospital mortality (51.9% versus 14.3%; $P < 0.001$) were higher in the CA-KPM group. In conclusion, diabetes mellitus and liver cirrhosis are more common in the CA-KPM patients who were also more likely to present with severe manifestations and poor outcomes.

1. Introduction

Community-acquired bacterial meningitis still remains one of the most feared infectious diseases, as it is often associated with substantial mortality and long-term neurologic complications. In adult patients, the most common pathogens for meningitis are *Streptococcus pneumoniae* and *Neisseria meningitidis* (Durand et al., 1993; Hussein and Shafran, 2000; Okike et al., 2014; Thigpen et al., 2011). The aerobic gram-negative bacilli are known as the significant pathogen to cause community-acquired meningitis in immunocompromised patients or in individuals older than 50 years (van de Beek et al., 2012). Epidemiologic trends between western and eastern countries appear to differ in the percentage contributions of gram-negative bacilli and the major species inducing meningitis. In surveys from western countries, aerobic gram-negative bacilli account for 4.3–12.3% of the pathogens causing bacterial meningitis (Cabellos et al., 2009; Durand et al., 1993; Hussein and Shafran, 2000; Okike et al., 2014; Thornorethardottir et al., 2014), with *Escherichia coli* as the leading pathogen among them. In Asia, the overall incidence of meningitis caused by gram-negative bacilli is 7.6–28.8% (Chan et al., 2002; Chang et al., 2008; Hui et al., 2005; Lu et al., 2000; Moon et al., 2010; Tang et al., 1999), which is about twice the incidence in the western countries, and among the implicated gram-negative pathogens, *Klebsiella pneumoniae* is the most common. Several studies by Taiwanese researchers have reported that *K. pneumoniae* meningitis (KPM) is often associated with male gender, diabetes mellitus, alcoholism, and liver cirrhosis (Lee et al., 2003; Lu et al., 2002; Tang et al., 1997). KPM-associated mortality in these reports has a wide range (33–93%) (Fang et al., 2000; Jang et al., 1993; Lee et al., 2004; Lu et al., 2002; Tang et al., 1997). However, these earlier studies have several limitations. First, they do not distinguish between acquisition sites; community-acquired and hospital-acquired cases, including postneurosurgical meningitis, are often grouped together (Lu et al., 2002; Tang et al., 1997). Second, one of these studies didn't distinguish between meningitis in adults and children (Tang et al., 1997). Finally, most previous studies fail to include adequate controls. In a recent Korean multicenter analysis, *K. pneumoniae* ranked third as the cause of all community-acquired bacterial meningitis, followed by *S. pneumoniae* and *Staphylococcus aureus* (Moon et al., 2010). This observation suggests that *K. pneumoniae* is also a significant cause of meningitis in South

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Korea. Since *S. pneumoniae* meningitis (SPM) is the best known type of bacterial meningitis, we speculated that important characteristics of KPM may emerge through a comparison with SPM. Therefore, using patients with community-acquired SPM (CA-SPM) as controls, we characterized the clinical and laboratory features of community-acquired KPM (CA-KPM) in adult patients in our current study.

2. Materials and methods

2.1. Patients

This multicenter retrospective cohort study involved patients from 8 general hospitals within the Republic of Korea. Using our institutional clinical microbiology computerized databases, all patients whose cerebrospinal fluid (CSF) culture yielded *K. pneumoniae* or *S. pneumoniae* between January 1997 and March 2013 were identified. Among these cases, adult patients (≥16 years old) with clinical meningitis acquired from the community were included in the analysis.

2.2. Data collection

Clinical information including patient demographics, underlying disease and medical conditions, clinical manifestations, initial laboratory results including CSF profiles, results of an antimicrobial susceptibility test, and the prescribed antimicrobial therapy was obtained from the patients' medical records. The outcomes assessed included the length of intensive care unit (ICU) stay, the length of hospital stay, mortality, and the presence of neurologic sequelae at discharge. Microbiologic identification and antimicrobial susceptibility tests were performed using various automated systems in each hospital. The study was approved by each respective hospital institutional review board, and the requirement for informed consent was waived due to the retrospective nature of the analysis.

2.3. Definitions

Bacterial meningitis was diagnosed if all of the following criteria applied: i) isolation of *K. pneumoniae* or *S. pneumoniae* in 1 or more CSF cultures; ii) typical CSF findings including pleocytosis, decreased glucose level, and increased protein concentration; and iii) clinical manifestations including fever, change in mental status, and meningismus (Lu et al., 2002).

Community-acquired meningitis was defined as meningitis that occurred within 48 hours of admission without a prior history of hospital admission or neurosurgical treatment within the previous year (Moon et al., 2010). Patients with risk factors for healthcare-associated infection and those with indwelling foreign devices, such as ventriculoperitoneal shunts, or those meeting the criteria for a nosocomial infection according to the CDC criteria were excluded (Garner et al., 1988). Focal neurologic signs included dilated nonreactive pupils, abnormalities of ocular motility, abnormal visual fields, gaze palsy, and arm or leg drift (Tunkel et al., 2004). Appropriate antimicrobial therapy was defined as the administration of 1 or more antimicrobial agents shown to be effective against bacterial pathogens in susceptibility tests and capable of passing through the blood–brain barrier at appreciable levels (Lu et al., 2002).

2.4. Statistical analysis

Data were analyzed using IBM SPSS for Windows (version 20.0; SPSS, Chicago, IL, USA). Results were expressed as the median (interquartile range [IQR]). Either the chi-square test or Fisher's exact test was used to compare categorical variables, and the Student's *t* test or the Mann–Whitney *U* test was used to compare continuous variables, as appropriate. A *P* value of less than 0.05 was considered statistically significant. Survival curves for patients with CA-KPM and CA-SPM were prepared according to the Kaplan–Meier method. The log-rank test was used to determine significance between the 2 survival curves.

Table 1
Demographic features and predisposing conditions of the 83 study patients with CA-KPM or CA-SPM.

	CA-KPM	CA-SPM	*P* value	All
	n = 27	n = 56		n = 83
Sex, male, n (%)	15 (55.6)	31 (55.4)	0.99	46 (55.4)
Age, median years (range)	59 (22–84)	59 (16–98)	0.23	59 (16–98)
Underlying diseases, n (%)				
Diabetes mellitus	13 (48.1)	12 (21.4)	0.01	25 (30.1)
Alcoholism	6 (22.2)	5 (8.9)	0.10	11 (13.3)
Solid tumor	4 (14.8)	6 (10.7)	0.72	10 (12.0)
Liver cirrhosis	6 (22.2)	3 (5.4)	0.05	9 (10.8)
Sinusitis	0 (0.0)	4 (7.1)	0.30	4 (4.8)
Chronic otitis media	1 (3.7)	3 (5.4)	1.00	4 (4.8)
Chronic obstructive pulmonary disease	0 (0.0)	3 (5.4)	0.55	3 (3.6)
Congestive heart failure	0 (0.0)	2 (3.6)	1.00	2 (2.4)
Hematologic malignancy	0 (0.0)	1 (1.8)	1.00	1 (1.2)

3. Results

3.1. Patient characteristics

A total of 83 adult patients were identified with community-acquired meningitis confirmed by a positive CSF culture for *K. pneumoniae* or *S. pneumoniae*. Twenty-seven (32.5%) patients had CA-KPM, and 56 (67.5%) patients had CA-SPM. During the study period, 3873 patients had community-acquired *K. pneumoniae* bacteremia, 716 patients had community-acquired *S. pneumoniae* bacteremia, and 1013 patients had community-acquired *K. pneumoniae* liver abscess. The demographic characteristics and underlying conditions of these patients are summarized in Table 1. Men accounted for 55.4% of all patients, and the median age of both groups was 59 years (range, 16–98 years). All patients were Korean, except for 1 Japanese man. When compared to the CA-SPM group, diabetes mellitus (CA-KPM, 48.1% versus CA-SPM, 21.4%, $P = 0.01$) and liver cirrhosis (CA-KPM, 22.2% versus CA-SPM, 5.4%, $P = 0.05$) were more common in the CA-KPM group. Chronic alcoholism tended to be more common in patients with CA-KPM (22.2% versus 8.9%, $P = 0.10$).

3.2. Clinical manifestations, initial laboratory findings, and CSF profiles

The clinical manifestations and laboratory data for the study patients are summarized in Table 2. Fever (CA-KPM, 85.2% versus CA-SPM, 75.0%, $P = 0.29$) and headache (CA-KPM, 59.3% versus CA-SPM, 75.5%, $P = 0.14$) were common symptoms in both groups. When compared to the CA-SPM group, concomitant extrameningeal infection was more common in the CA-KPM group (40.7% versus 7.1%, $P = 0.001$). Of 11 CA-SPM patients who had an extrameningeal infection, 9 had concomitant pneumonia, 4 had a liver abscess, 2 had endophthalmitis, and 1 had a brain abscess. Three patients had 2 concomitant extrameningeal infections, and 1 patient had 3 concomitant extrameningeal infections. More patients initially presented with septic shock (44.4% versus 8.9%, $P < 0.001$) and comatose mental status (40.7% versus 12.5%, $P = 0.01$) in the CA-KPM group. Similarly, the initial median Glasgow Coma Scale score was significantly lower in the CA-KPM group (7 [IQR, 3–15] versus 9 [IQR, 3–15]; $P = 0.01$). Concomitant bacteremia was present in 65.4% of the CA-KPM group versus 43.6% of the CA-SPM group, respectively ($P = 0.07$). Concomitant bacteriuria was also significantly more common in the CA-KPM group than the CA-SPM group (50% versus 8.1%, $P < 0.001$).

Neither the median value of total CSF white blood cell (WBC) counts and polymorphonuclear cell counts, nor CSF protein and glucose level