Culture-proven Bacterial Meningitis in Elderly Patients in Southern Taiwan: Clinical Characteristics and Prognostic Factors

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Abstract- The epidemiologic landscape of causative pathogens and clinical characteristics of bacterial meningitis varies with several clinical factors including preceding/pre-existent medical and/or surgical conditions, modes of contraction, geographic distributions, status of vaccinations, the study time periods and differences among age groups. In order to delineate the epidemiology of bacterial meningitis in senior adults (ages ≥60 y/o) in southern Taiwan, we analyzed the clinical characteristics and therapeutic outcomes of 64 senior adults (42 men and 22 women, aged 60-80 years) with bacterial meningitis collected over a period of 13 years at our hospital. The prognostic factors between fatal and non-fatal groups of patients were compared. Twenty-seven of the 64 patients belonged to a nosocomial infection group, and the other 37 comprised a community-acquired infection group. Sixty percent (39/64) of the patients had a post-neurosurgical state as the most preceding event prior to infection. Liver disease (13) and diabetes mellitus (6) were the most common underlying conditions of the other 25 patients with spontaneous meningitis. Of these 64 patients, *Klebsiella (K.) pneumoniae* (18), *Acinetobacter baumannii* (5), *Escherichia coli* (5), and *Enterobacter species* (5) were the most commonly implicated Gram-negative pathogens. *Staphylococcus (S.) aureus* infection was increasing during the study period. The therapeutic results of this group of patients showed a mortality rate of 38% (24/64). The presence of septic shock was the most significant prognostic factor. In conclusion, for this study group, a post-neurosurgical state was the single most important preceding event for senior adults developing bacterial meningitis. Of the implicated pathogens, *K. pneumoniae* and *S. aureus* were the most common gram-negative and gram-positive pathogens, respectively. The therapeutic result of this specific group of patients showed a high mortality rate; however, the small case number and possible bias of case selection have limited the analytical conclusions of this study.

Key Words: *Klebsiella pneumoniae*, Meningitis, Old-aged adults, Postneurosurgical state, *Staphylococcus aureus*

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INTRODUCTION

The prevalence rate of causative pathogens of bacterial meningitis varies with several clinical factors including preceding medical and/or surgical conditions, mode of contraction, geographic distribution, status of

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vaccination, the study time period and age[1-4]. It is well known that older patients with infections, including bacterial meningitis, may present with fewer classic signs and symptoms. Because of clinical ignorance, older patients may delay treatment of devastating infectious diseases and thereby risk a grave outcome. Acute bacterial meningitis is one of the infectious diseases that needs rapid and appropriate antibiotic treatment in order to ensure better therapeutic results[5]. The choice of initial empiric antibiotics is usually guided by the epidemiologic trend of causative pathogens in a specific group of patients. However, there are rare reports dealing with bacterial meningitis in senior adults[6-8]. In this study we analyzed the epidemiologic trend of bacterial meningitis in adult patients over 60 years of age in order to delineate the clinical characteristics of this specific group of patients in southern Taiwan.

METHODS

We retrospectively reviewed the microbiological records of cerebrospinal fluid (CSF) and blood cultures, other laboratory data and medical records of adult patients (≥17 years old) with culture-proven bacterial meningitis admitted to Chang Gung Memorial Hospital (CGMH)-Kaohsiung over a period of 13 years (January 1991 - December 2003). CGMH-Kaohsiung, the largest medical center in southern Taiwan, is a 2482-bed acute-care teaching hospital, which provides both primary and tertiary referral care. Southern Taiwan consists of two cities and three counties with an old-aged population of approximately 724,840 as of October 2003. The annual population increase for the aged population is reported to be about 2.3%[9]. During the study period, 294 adult patients were identified to have culture-proven bacterial meningitis. Sixty-four of these 294 adult patients, aged ≥60 years old ("older aged group") were included in this study for further analysis.

In this study, the criteria for a definite diagnosis of adult bacterial meningitis (ABM) included the following: (1) Positive CSF culture of bacterial pathogen(s); (2) Clinical features of meningitis including fever, consciousness disturbance, seizure, and signs of meningeal irritation; and, (3) Purulent CSF features including at least one of the following parameters: leukocytosis with leukocyte count $>0.25 \times 10^9$/L and predominant polymorphonuclear cells; lactate concentration >3.5 mmol/L; and, glucose ratio (CSF glucose/serum glucose) <0.4 or glucose level <2.5 mmol/L if no simultaneous blood glucose level was determined. As viridans streptococci and coagulase-negative staphylococci (CoNS) are common contaminants of cultures, the diagnosis of meningitis caused by these two groups of pathogens was defined with more strict criteria[1,10,11], only if repeated CSF cultures demonstrated positive results or if they were cultured from the tip of an indwelling neurosurgical device. Patients with evidence of concomitant chronic meningitis or encephalitis, not due to bacterial pathogens, were excluded from this study. Patients were considered to have "mixed bacterial meningitis" if at least two bacterial organisms were isolated from the initial CSF culture[12].

For the purposes of this study, ABM cases were classified into one of two groups: As either being nosocomial or community-acquired infection. "Nosocomial" meningitis was defined as bacterial infection not present when the patient was admitted to the hospital, clinical evidence of an infection no sooner than seven days after admission, or clinical evidence of meningitis within a short period of time, usually within one month after discharge from the hospital where the patient had received an invasive procedure, especially a neurosurgical procedure. Otherwise, the patient was considered to have "community-acquired" infection. Patients who developed meningitis related to head trauma with skull fractures, neurosurgical procedures, or skull base lesions including neoplasm invasion were classified with "post-neurosurgical" meningitis. Otherwise, patients who demonstrated no clear distinctive disease characteristics and who had not undergone any invasive procedures were classified with "spontaneous" meningitis.

In this study, the initial consciousness level for adult patients was classified into four groups: I) Normal consciousness (Glasgow coma scale (GCS) score = 15); II) Inattention, confusion, and clouding of consciousness (GCS score = 10-14); III) Stupor (GCS score = 4-9); and IV) Coma (GCS score = 3). "Leukocytosis" was defined

as a peripheral white blood cell (WBC) count $>10\times10^9$/L, "leukopenia" as a WBC count $<5\times10^9$/L, and "thrombocytopenia" as a platelet count $<140\times10^9$/L. Bacteremia was considered as "positive" only when multiple blood cultures grew the same bacterial pathogen. "Shock" was defined as a clinical syndrome that resulted from inadequate tissue perfusion and the existence of hypotension, i.e., a mean arterial pressure <60 mmHg. Over the study period, intravenous administration of penicillin G or vancomycin with one of the third generation cephalosporins (ceftriaxone, ceftazidime) or cefepime were the initial empiric antibiotics used in the treatment of adult patients with clinical evidence of bacterial meningitis in our hospital. Further, antibiotic adjustment was guided according to the results of pathogenic identification and antibiotic susceptibility tests. Antibiotic susceptibility of the isolated pathogen was tested using the Kirby-Bauer diffusion method (BBL, Muller-Hinton II agars; Becton Dickinson Microbiology Systems, Cockeysville, MD). The other antibiotics including oxacillin, imipenem and meropenem were used for antibiotic adjustment after the final results of bacterial culture and antibiotic susceptibility test were available.

For statistical analysis, the 64 patients were divided into two outcome groups (fatal and non-fatal). Data including gender, type of acquisition of infection, type of infection, underlying conditions, clinical manifestations, laboratory data and therapeutic outcomes between these two patient groups were analyzed by means of a Chi-square test or Fisher's exact test. Age difference between the two patient groups was analyzed by means of a Student's t-test. CSF data for the WBC counts, glucose, total proteins and lactate concentrations for the two patient groups were analyzed by means of Wilcoxon rank sum test. Multiple logistic regression analysis was used to evaluate the relationships among variables and the two patient groups adjusted for other potential confounding factors. Variables with zero cell counts were eliminated for logistic analysis, and only variables with statistical significance ($p < 0.05$) were included in the final model. All analyses were conducted using SAS (SAS Statistical Institute, 1990)[13].

RESULTS

The causative pathogens and clinical characteristics of these 64 old-aged patients are listed in Tables 1-4. The 64 patients were 42 men (mean age, 67.9 years, range, 60-80) and 22 women (mean age, 68.5, range, 60-79). Twenty-seven of these 64 patients contracted the infection nosocomially, and the other 37 had community-acquired infection. A post-neurosurgical state as the preceding event was found in 39 of these 64 patients, while the other 25 patients had spontaneous meningitis. Of the post-neurosurgical states, hydrocephalus sp ventriculoperitoneal (VP) shunt or external ventricular device (EVD) were the most common. Among the 39 patients with a post-neurosurgical bacterial meningitis state, 8 also had diabetes mellitus (DM). Of the 25 patients with spontaneous meningitis, hepatobiliary disorder and DM were the common underlying conditions. As to the clinical manifestations in these 64 patients, altered consciousness (54) and fever (54) were most common, followed by seizure (23), hydrocephalus (18), shock (15) and headache (14).

The causative pathogens of these 64 patients are listed in Table 1. *Klebsiella (K.) pneumoniae* (18) was the most commonly implicated pathogen and all *K. pneumoniae* meningitis patients had community-acquired infection. Of these 18 cases with *K. pneumoniae* meningitis, 4 had DM, 8 had liver disease, and 3 had both DM and liver disease. *Staphylococcus (S.) aureus* was the second most common pathogen (7) and most of them emerged in the later years of the study period. Five of the 7 implicated *S. aureus* strains were methicillin-resistant strains (MRSA). All 7 cases with *S. aureus* meningitis had a post-neurosurgical state as the underlying condition. All 5 cases with mixed bacterial infection had a post-neurosurgical state as the underlying condition. *Streptococcus pneumoniae* infection was noted in two cases and they all appeared in the first study period.

In this study, 24 of the 64 patients died. Of the clinical factors (Tables 3 and 4), shock, thrombocytopenia, and high CSF white cell count and lactate level had statistical significance on prognosis. Variables used for the stepwise logistic regression including the above-men-

Table 1. *Causative pathogens of bacterial meningitis of the 64 older aged patients*

	1991 - 1997 N = 19	1998 - 2003 N = 45	Total N = 64	Case fatality N = 24	Community acquired	Nosocomial δ
Klebsiella pneumonia	5 (4)	13 (5)	18	9	18	0
Staphylococcus aureus	1 (1)	6 (1)	7	2	2	5
Coagulase-negative staphylococcus	1 (0)	1 (0)	2	0	0	2
Group A Streptococci	0 (0)	1 (0)	1	0	0	1
Group B Streptococci	1 (1)	0 (0)	1	1	1	0
Enterococcus	1 (0)	0 (0)	1	0	0	1
Streptococcus pneumonia	2 (0)	0 (0)	2	0	2	0
Viridans streptococci	0 (0)	2 (0)	2	0	2	0
Corynebacterium species	0 (0)	1 (0)	1	0	0	1
Pseudomonas aeruginosa	1 (0)	1 (0)	2	0	1	1
Acinetobacter baumannii	0	5 (3)	5	3	1	4
Escherichia coli	3 (2)	2 (1)	5	3	2	3
Enterobacter species	2 (0)	3 (1)	5	1	1	4
Proteus mirabilis	0 (0)	3 (1)	3	1	1	2
Serratia marcescens	1 (1)	1 (1)	1	1	0	1
Salmonella Group B	0 (0)	2 (0)	2	0	2	0
Citrobacter diversus	0 (0)	1 (0)	1	0	1	0
Mixed infection	1 (1)	4 (2)	5	3	2α	3β,γ

( ): Values in parentheses indicate number of fatalities

α : Klebsiella pneumoniae, Escherichia coli, Group D streptococci, Bacteroides fragilis; Pseudomonas aeruginosa, Citrobacter diversus

β : Pseudomonas aeruginosa, Acinetobacter species.

γ : Enterococcus faecalis, Acinetobacter species; Acinetobacter species, Staphylococcus aureus (only one case of recurrent infection)

δ : Third generation cephalosporin-resistant Gram-negative bacillary meningitis was found in three patients, and oxacillin resistant Staphylococcus aureus was found in four patients.

Table 2. *Underlying conditions*

Postneurosurgical form α (n = 39)	N	Spontaneous form α (n = 25)	n
Hydrocephalus s/p VP shunt or EVD	20	Diabetes mellitus	6
Spontaneous ICH s/p craniotomy	17	Alcoholism	3
Head injury without operation	5	Unknown(none)	3
Head injury s/p craniotomy	5	Abnormal liver function test	10
Acute ischemic stroke s/p craniotomy	2	Liver cirrhosis	3
Diabetic mellitus	8	NPC	1
Spinal injury s/p operation	3	Spontaneous ICH	1
Old ischemic stroke	3	Sphenoid sinusitis and mastoiditis	1
Cervical spine laminectomy and craniectomy	1	ESRD	2
Chronic otitis media and paranasal sinusitis s/p operation	1	Chronic otitis media or paranasal sinusitis	3
NPC with skull base defect	1	Old ischemic stroke	4
Myelogram	1	Gall stone	6
Acoustic neuroma s/p craniotomy	1		
Alcoholism	1		
Syphilis	1		

VP: ventriculoperitoneal; EVD: external ventricular device; ICH: intracerebral hemorrhage; ESRD: end stage renal disease; NPC: nasopharyngeal carcinoma.

Table 3. *Prognostic factors of bacterial meningitis of the 64 older aged patients*

	Non-fatal N=40	Fatal N=24	P-value	OR	95% CI
(1) Age at infection	68.5 ±5.22	67.9 ±5.86	0.712		
(2) Sex					
Male	27	15	0.683	0.802	0.278-2.313
Female	13	9			
(3) Types of infection					
Spontaneous	14	11	0.390	1.571	0.559-4.414
Post neurosurgical status	26	13			
(4) Acquisition of infection					
Communit-acquiredy	25	13	0.511	1.410	0.505-3.938
Nosocomial	15	11			
(5) Initial level of consciousness					
Group I	8	2	0.282	0.098	0.058-0.691[a]
Group II	16	8		0.17	0.198-0.587[a]
Group III	16	13		0.27	0.299-0.671[a]
Group IV	0[c]	1			
(6) Underlying conditions					
Diabetes mellitus					
Yes	11	5	0.551	0.694	0.208-2.315
No	45	11			
Alcoholism					
Yes	4	0[c]	0.288		
No	36	24			
(7) Clinical manifestation					
Fever					
Yes	35	19	0.482	0.543	0.139-2.114
No	5	5			
Headache†					
Yes	11	3	0.316	0.436	0.097-1.958
No	16	10			
Shock					
Yes	4	11	0.001*	7.615	2.058-28.178
No	36	13			
Seizure					
Yes	12	11	0.201	1.974	0.691-5.641
No	28	13			
HHNK or DKA					
Yes	1	2	0.551	3.545	0.304-41.362
No	39	22			
Hydrocephalus					
Yes	8	10	0.062	2.857	0.930-8.774
No	32	14			
Intracranial focal suppuration					
Yes	11	3	0.160	0.377	0.093-1.519
No	29	21			
(8) Peripheral blood study†					
Bacteremia					
Yes	11	9	0.567	1.385	0.453-4.228
No	22	13			
Thrombocytopenia					
Yes	6	10	0.017*	4.408	1.234-13.281
No	34	14			
White blood cell count					
> 10 $\times 10^9$/L	31	14	0.092	0.092	0.201-0.481[b]
10 -4 $\times 10^9$/L	9	8		0.6	0.284-0.779[b]
< 4 $\times 10^9$/L	0[c]	2			

HHNK: hyperosmolar hyperglycemic nonketotic syndrome; DKA: diabetic ketoacidosis; OR: odds ratio; CI: confidence interval; †: not every patient had every test; *: statistically significant; a: relative to group IV; b: relative to <4 $\times 10^9$/L; c: using a correction of 0.5 in every cell that contains a zero

Table 4. *Mean values ±S.D. of initial cerebrospinal fluid protein, glucose, lactate and leukocyte count*

	No. of patients†	Glucose (mmol/L)	Total Protein (g/L)	Lactate (mmol/L)	White cell count (10^9/L)
Fatal	n = 24	1.5 ±2.1	5.1 ±4.7	18.8 ±9.8	8.5 ±14.5
		n = 18	n = 18	n = 17	n = 17
Non-fatal	n = 40	2.8 ±3.1	3.9 ±3.5	13.6 ±10.6	4.4 ±11.2
		n = 27	n = 26	n = 25	n = 27
P value		0.179	0.159	0.044*	0.044*

†: Not all patients had every test; *: Statistically significant.

tioned clinical factors showed that only presence of septic shock (*P*=0.004) was independently associated with high mortality.

DISCUSSION

These 64 older aged ABM patients accounted for 22% (64/294) of our culture-proven ABM. Sixty percent (39/64) of these patients had a post-neurosurgical state (one with nasopharyngeal carcinoma and skull base invasion), a process that may disrupt the mechanical barrier of central nervous system (CNS), as their underlying condition of bacterial meningitis. Fifty-six percent (36/64) of these older aged patients had community-acquired infection and the other 44% patients contracted the infection nosocomially. The relatively high incidence of post-neurosurgical state as the preceding event in this group of patients differs greatly with that of our ABM patients in the overall age group[3] and those of other reports[1,2,4]. The possible causes of the high incidence of ABM in the post-neurosurgical state group of patients may be as follows: (1) A post-neurosurgical state is one of the common conditions that may interrupt the defensive barrier of CNS of older patients; (2) There is an increasing frequency of neurosurgical procedures in our hospital because of the increasing number of neurosurgeons, the improvement in neurosurgical facilities and the larger number of patients with neurosurgical conditions[14]; and (3) An inadequate infection control program may exist in the hospital[15]. However, this finding suggests that a post-neurosurgical state is an important preceding event for older patients in developing bacterial meningitis.

In this study, fever (84%) and consciousness disturbance (84%) were the major clinical presentations. The clinical characteristics of the 64 older aged ABM patients were not unique and were similar to those with ABM in the overall age group[3]. Therefore, in senior patients with fever and altered consciousness, the diagnosis of bacterial meningitis should be highly suspected. Early confirmation of diagnosis and early administration of appropriate antibiotic are essential for the management of this specific group of ABM patients.

DM and liver disease are known risk factors for the development of infections, including meningitis[16-19]. In this study, 83% (15/18) of the *K. pneumoniae* infection had DM and/or liver disease. *K. pneumoniae* is also the most commonly implicated pathogen of elderly patients with bacterial meningitis. This finding is consistent with those of other reports[18,20,21] in which they showed *K. pneumoniae* as the most common causative pathogens of community-acquired ABM in Taiwan, especially in those patients with DM and/or liver disease and spontaneous infection. In this study, the other commonly implicated Gram-negative pathogens were *A. baumannii*, *E. coli* and *Enterobacter spp*. and most of the patients contracted these pathogens nosocomially. These Gram-negative pathogens are also known as common pathogens of ABM of adult patients with nosocomial post-neurosurgical infection[22-24]. In this study, *S. aureus* was the most common Gram-positive pathogen of ABM of older aged patients and all the patients contracted the infection nosocomially. Seventy-one percent (5/7) of the isolated *S. aureus* strains were methicillin-resistant. The high incidence of MRSA in this group of patients may be related to the high incidence of post-neurosurgical states,

and most of the MRSA strains have emerged in recent years[15,25]. This increase in adult MRSA meningitis is consistent with the reported findings of rapid dissemination of *S. aureus* with classic oxacillin resistance, especially in patients with nosocomial infections in Taiwan[26,27]. For the recent emergence and increasing incidence of MRSA strains in senior ABM patients, vancomycin, at least, should be considered as one of the initial empiric antibiotics in the management of this specific group of patients if culture and antibiotic susceptibility test are not available. In this study, *Streptococcus pneumoniae*, a common pathogen of community-acquired ABM in both western and eastern countries[1,20], was not a common pathogen within this group of patients, and all of them occurred in the earlier years of the study period. The exact cause of low incidence of *Streptococcus pneumoniae* infection in this group of patients in recent years is not clear, a high incidence of post-neurosurgical state as a preceding event in this group of patients may be a possible explanation because *Streptocous pneumoniae* is not a common pathogen of post-neurosurgical ABM. Mixed bacterial meningitis was also common in this group of patients and most of the cases appeared in the later study period, especially in patients with a post-neurosurgical state as the underlying condition. This finding is consistent with our previous study results[12].

In this study, the overall mortality rate of this specific group of patients was 38% (24/64). Of the several potentially prognostic factors including shock, thrombocytopenia, high CSF white cell count and elevated lactate level, shock was the most important one. This finding is in accordance with previous study results[3,20] and may suggest the importance of early diagnosis and early treatment of this specific group of ABM patients.

In conclusion, a post-neurosurgical state is one of the important preceding events for older aged or senior patients in developing bacterial meningitis. In this group of patients, *K. pneumoniae* and *S. aureus* are the most commonly implicated Gram-negative and Gram-positive pathogens, respectively. *K. pneumoniae* infection is found especially in community-acquired infections while *S. aureus*, in the nosocomial infections. In recent years, there is an increasing MRSA infection in the senior ABM patients. Therefore, vancomycin, at least, should be considered as one of the initial empiric antibiotics in the management of this specific group of patients. The clinical characteristics of the senior ABM patients were not unique and can be found in ABM of the overall age group. Bacterial meningitis in this group of patients still has high mortality rate. Of the prognostic factors, the presence of shock precludes a grave therapeutic result. The finding may suggest the importance of early diagnosis and early treatment in senior patients with bacterial meningitis.

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