Mixed Infection in Adult Bacterial Meningitis

W.N. Chang, C.H. Lu, C.R. Huang, Y.C. Chuang

Summary

12 adult patients suffering from bacterial meningitis caused by mixed infection were identified at Kaohsiung Chang Gung Memorial Hospital over a period of 13 years (1986–1998), and they accounted for 6.5% (12/184) of our culture-proven adult bacterial meningitis. The 12 cases included seven males and five females, aged 17–74 years. Six of the 12 cases had community-acquired infections and the other six had nosocomially-acquired infections. Ten of the 12 cases had associated underlying diseases, with head trauma and/or neurosurgical procedure being the most frequent. Both gram-negative and gram-positive pathogens were identified in these 12 cases with gram-negative pathogens outnumbering the gram-positive ones. The implicated pathogens, starting with the most frequent, included *Enterobacter* species (*Enterobacter cloacae, Enterobacter aerogenes*), *Klebsiella* species (*Klebsiella pneumoniae, Klebsiella oxytoca*), *Escherichia coli*, *Staphylococcus* species (*Staphylococcus aureus, Staphylococcus haemolyticus*), *Pseudomonas aeruginosa, Acinetobacter baumannii, Enterococcus, Serratia marcescens, Citrobacter diversus, Proteus mirabilis, Streptococcus viridans* and *Neisseria meningitidis*. Six of the 12 cases were found to have multi-antibiotic-resistant strains, which included *E. cloacae* in one, *A. baumannii* in one, *K. pneumoniae* in one and *S. aureus* in three. The management of these 12 cases included appropriate antibiotics and neurosurgical procedures including shunt revision. Despite the complexity of implicated pathogens and the high incidence of emergence of resistant strains, the overall mortality rate (8.3%, 1/12) was not higher than that in adult bacterial meningitis. However, complete recuperation was difficult in adult patients with mixed bacterial meningitis.

Key Words

Adult bacterial meningitis · Mixed infection · Nosocomial infection · Postneurosurgical state

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Introduction

Bacterial meningitis is an infectious disease of worldwide distribution and its causative pathogens have varied over various periods of time, geographic distribution, age, underlying medical and/or surgical condition, and means of contraction [1, 2]. Mixed infection in bacterial meningitis has been documented in some reports [3–7] but has been rarely examined in the literature. There is an increasing incidence of mixed bacterial meningitis in adults and the common predisposing factors include infection at contiguous foci, tumors in close proximity to the central nervous system (CNS), and fistulous communications with the CNS [4]. Over a period of 13 years, 12 adult meningitis patients with mixed infections were identified in our hospital. Their causative pathogens, clinical manifestations and therapeutic outcome were analyzed in this study.

Patients and Methods

Over a period of 13 years (1986–1998), 184 adult cases with culture-proven bacterial meningitis were identified at Kaohsiung Chang Gung Memorial Hospital. Of these 184 cases, 12 were found to have mixed infections identified by means of positive cerebrospinal fluid (CSF) culture and thus included in this study in which we analyzed their implicated bacterial organisms, clinical manifestations, associated medical and/or surgical conditions and therapeutic outcomes. A definite diagnosis of bacterial meningitis was defined as either isolation of a specific bacterial pathogen in one or more CSF cultures and clinical features of acute meningitis, or isolation of a specific bacterial pathogen in blood culture with clinical manifestations of acute meningitis and typical CSF findings including decreased glucose level, increased lactate and protein concentration and pleocytosis with predominant polymorphonuclear (PMN) cells. The term "mixed infection" was defined as having at least two distinct bacterial organisms isolated from the initial CSF cultures.

"Nosocomial meningitis" was defined as bacterial infection that was not present when the patient was admitted to the hospital, or clinical evidence of infection no sooner than 48 h after ad-

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mission. Patients who developed meningitis related to head trauma with skull fracture or neurosurgical procedures were classified as having a postneurosurgical form. Otherwise, patients who presented no clearly distinctive characteristics and who had not received invasive procedures were classified as having a spontaneous form. Patients with evidence of concomitant chronic meningitis or encephalitis not due to bacterial pathogens were excluded from this study.

Antibiotic susceptibility was tested by the Kirby-Bauer disk diffusion method (Becton Dickinson, BBL Mueller-Hinton II agar). Appropriate antibiotic therapy was defined as the administration of one or more antimicrobial agents shown to be effective against bacterial pathogens by susceptibility tests and shown to be capable of passing through the blood-brain barrier in adequate amounts, commencing either on the day of admission or before the deterioration of neurological and systemic conditions of the inpatients.

Results

The 12 cases included seven males and five females, aged 17–74 years (mean age 44). The basic clinical and labora-

Table 1
Basic clinical data of patients.

Pt	Age(yr)/ Sex	CSF culture	Antibiotic treatment Dosage	Length of treatment(days)	Underlying diseases	Infectious pattern	Clinical manifestation
1	33/F	*Enterobacter aerogenes, Enterobacter cloacae*	Penicillin G 24 x 10^5 U/day, i.v.; Chloramphenicol 4 g/day, i.v.	14	(–)	Community-acquired	Fever
2	41/M	*Klebsiella pneumoniae, Escherichia coli*	Penicillin G 24 x 10^5 U/day, i.v.; Moxalactam 6 g/day, i.v.	14	(–)	Community-acquired	Altered consciousness, fever
3	61/F	*Pseudomonas aeruginosa, Escherichia coli, Enterococcus*	Penicillin G 24 x 10^5 U/day, i.v.; Ceftazidime 6 g/day, i.v.	63	SAH s/p craniotomy V-P shunt	Community-acquired	Altered consciousness, fever, hydrocephalus
4	58/M	*Klebsiella oxytoca Escherichia coli*	Penicillin G 24 x 10^5 U/day, i.v.; Moxalactam 8 g/day, i.v.	65	COM	Community-acquired	Altered consciousness, fever
5	30/M	*Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae, Streptococcus viridans*	Penicillin G 24 x 10^5 U/day, i.v.; Ceftazidime 6 g/day, i.v.	30	Traumatic ICH s/p V-P shunt	Community-acquired	Fever, hydrocephalus
6	17/M	*Citrobacter diversus, Escherichia coli, Staphylococcus aureus*	Vancomycin 1.5 g/day, i.v.; Ceftazidime 6 g/day, i.v.	28	Traumatic ICH s/p V-P shunt	Nosocomial	Fever, hydrocephalus
7	21/M	*Pseudomonas aeruginosa, Neisseria meningitidis, Enterococcus, Staphylococcus aureus*	Vancomycin 2 g/day, i.v.; Ceftazidime 6 g/day, i.v.	39	Traumatic ICH s/p V-P shunt	Community-acquired	Altered consciousness, fever, hydrocephalus, seizure
8	59/F	*Enterobacter cloacae, Serratia marcescens*	IPM 1.5 g/day, i.v.	21	SAH s/p craniotomy V-P shunt	Nosocomial	Altered consciousness, fever, hydrocephalus
9	53/F	*Staphylococcus aureus, Staphylococcus haemolyticus*	Vancomycin 1.5 g/day, i.v.	32	Traumatic ICH s/p V-P shunt, DM	Nosocomial	Altered consciousness, fever, hydrocephalus
10	19/M	*Acinetobacter baumannii, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae*	IPM 3 g/day, i.v.	34	HI skull fracture, DM	Nosocomial	Altered consciousness, fever, hydrocephalus, seizure
11	74/F	*Acinetobacter baumannii, Pseudomonas aeruginosa*	Penicillin G 24 x 10^5 U/day, i.v.; Ceftazidime 6 g/day, i.v.	14[a]	SAH s/p craniotomy V-P shunt	Nosocomial	Altered consciousness, fever, hydrocephalus, seizure, septic shock
12	61/M	*Klebsiella pneumoniae, Enterobacter cloacae*	IPM 1.5 g/day, i.v.	21	Traumatic ICH s/p V-P shunt, DM	Nosocomial	Altered consciousness, fever, hydrocephalus, seizure

Pt: patient number; M: male; F: female; (–): no; yr: years old; CSF: cerebrospinal fluid; IPM: imipenem/cilastatin; i.v.: intravenous; [a] mortality; SAH: subarachnoid hemorrhage; ICH: intracerebral hemorrhage; V-P: ventriculo-peritoneal; COM: chronic otitis media; s/p: post status; HI: head injury; DM: diabetes mellitus

tory data of the 12 adult meningitis patients with mixed infection are listed in tables 1 and 2. Among these 12 cases, four were determined to have a spontaneous form and the other eight a postneurosurgical form. Patients 1, 2 and 4 had community-acquired meningitis. The meningitis of Patients 3, 5 and 7 was also considered to be community-acquired as these three patients had been discharged from hospital for 18, 90, and 6 months, respectively, when clinical evidence of meningitis occurred. Patients 6 and 8–12 were considered to have nosocomial meningitis because their infections occurred during hospitalization for neurosurgical problems. Totally, six patients had community-acquired meningitis and the other six had nosocomial meningitis.

Table 2
Basic laboratory data of patients.

Pt	Bacteremia	Peripheral leukocytosis	CSF			
			Glucose (blood glucose) (mg/dl)	Protein (mg/dl)	Lactate (mg/dl)	WBC count (cell/mm^3) (% PMN)
1	(–)	(–)	45 (105)	66.0	26.0	216 (97)
2	(–)	(–)	34 (90)	186.0	89.2	569 (79)
3	(–)	(+)	25 (110)	313.0	65.0	331 (90)
4	(+)[a]	(+)	13 (119)	133.0	82.0	3,460 (77)
5	(–)	(+)	2 (110)	1,616.0	269	71,000 (80)
6	(+)[b]	(+)	57 (110)	30.6	13.0	71 (65)
7	(–)	(+)	30 (106)	142.0	65.6	180 (87)
8	(–)	(–)	118 (175)	19.6	29.8	5 (80)
9	(–)	(+)	ND	ND	ND	520 (75)
10	(+)[c]	(+)	7 (140)	67.4	139.7	100 (90)
11	(–)	(+)	18 (92)	20.0	309.5	4,800 (97)
12	(–)	(+)	2 (380)	988	37.1	8,600 (88)

Pt: patient number; (–): negative; (+): positive; ND: incomplete data; CSF: cerebrospinal fluid; WBC: white blood cell; PMN: polymorphonuclear; [a] *Klebsiella oxytoca*, *Escherichia coli*; [b] *Citrobacter diversus*, *Escherichia coli*, *Staphylococcus aureus*; [c] *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Enterobacter cloacae*

The causative pathogens isolated from the CSF cultures of these 12 cases included *Enterobacter* species (*Enterobacter cloacae*, *Enterobacter aerogenes*), *Escherichia coli*, *Klebsiella* species (*Klebsiella pneumoniae*, *Klebsiella oxytoca*), *Staphylococcus* species (*Staphylococcus aureus*, *Staphylococcus haemolyticus*), *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Citrobacter diversus*, *Serratia marcescens*, *Proteus mirabilis*, *Enterococcus* and *Neisseria meningitidis*. Except for two cases (Patients 1 and 2), associated conditions were found in ten. Among the associated conditions, head injury and/or neurosurgical procedures were found in nine cases (Patients 3, 5–12). Patient 4 had chronic otitis media, and Patients 9, 10 and 12 had diabetes mellitus. Fever was the only consistent and shared clinical manifestation found in these 12 cases. The other clinical manifestations included conscious disturbance, hydrocephalus, seizures and septic shock. Except for three cases (Patients 1, 2 and 8), peripheral leukocytosis was found in the other nine. The levels of CSF glucose ranged from 2.0 to 118.0 mg/dl, total protein from 20.0 to 1,616.0 mg/dl, lactate from 13.0 to 309.5 mg/dl, and white blood cell (WBC) count from 5 to 71,000 cells/mm^3. Blood cultures were carried out in all 12 cases and bacteremia was found in three (Patients 4, 6 and 10). The organisms isolated from blood cultures were found to be the same as those found in CSF cultures of Patients 4 and 6, and partially the same as those found in CSF culture of Patient 10.

The antibiotics used in the treatment of these 12 cases are listed in table 1. Of these 12 cases, multi-antibiotic-resistant strains were found in six. Among these six cases with multi-antibiotic-resistant strains, three belonged to third-generation cephalosporin-resistant gram-negative bacilli (*E. cloacae* in Patient 8, *A. baumannii* in Patient 10, *K. pneumoniae* in Patient 12) and three (Patients 6, 7 and 9) belonged to oxacillin-resistant *S. aureus*. The resistant strains in Patients 8, 10 and 12 showed resistance to moxalactam, ceftazidime, cefotaxime and ceftriaxone, and retained their sensitivity to imipenem/cilastatin. The resistant strains in Patients 6, 7 and 9 showed resistance to penicillin and ampicillin, and retained sensitivity to vancomycin only. Besides appropriate antibiotic therapy, removal of previously existing ventriculo-peritoneal (V-P) shunt was carried out in Patients 3, 5–9 and 11, and insertion of a new V-P shunt was done in five cases (Patients 3, 5–8). An insertion of a V-P shunt was also carried out in Patients 10 and 12 to relieve hydrocephalus. Therapeutic results showed that Patients 1, 2, 5 and 6 were left in normal states, patient 3 was left with mild left hemiparesis, Patient 4 was left with dysphasia, Patients 7 and 12 were left in mildly decreased mental states, Patients 8–10 were left in vegetative states and Patient 11 died.

Discussion

Mixed infection is commonly found in focal suppuration of CNS [8, 9] but is rarely reported in adult bacterial meningitis. The clinical manifestations and CSF features of our 12 cases with mixed bacterial meningitis were not unique and were similar to those in other cases of adult bacterial meningitis caused by a single pathogen; therefore, the diagnosis could only be confirmed by bacterial culture from

CSF. Mixed infection accounted for 6.5% of our culture-proven adult bacterial meningitis, and this incidence of mixed infection in adult bacterial meningitis is consistent with the data of *Durand* et al. [7]. Associated underlying conditions were found in ten of the 12 cases, with head trauma and/or neurosurgical procedures being the most common. Head trauma and neurosurgical procedures may cause insult to the defenses of the CNS, which may render the host susceptible to infection [10]. From this point of view, head trauma and/or postneurosurgical procedures including the insertion of a V-P shunt are important predisposing factors for mixed infection in adult bacterial meningitis, a finding which is consistent with other reports [11–13].

The causative pathogens found in these 12 cases were protean. Both gram-negative and gram-positive pathogens were identified in these 12 cases with gram-negative pathogens outnumbering the gram-positive ones. Although *Enterobacter meningitis* is relatively uncommon in both community-acquired and nosocomially-acquired adult bacterial meningitis [7, 14], *Enterobacter* species, especially *E. cloacae*, were the most common pathogens found in our cases. *Klebsiella* species, especially *K. pneumoniae*, are the most common pathogens of adult gram-negative bacillary meningitis found in our hospital as well as in Taiwan [15, 16], and they were the second most common pathogens found in this study. *E. coli* was not a common pathogen among our adult patients with gram-negative bacillary meningitis [15], but it was a common pathogen among mixed bacterial meningitis found in this study. *Staphylococcus* species, especially *S. aureus*, were other common pathogens found in this study. Although *Staphylococcus* species are not common pathogens of adult bacterial meningitis, they have become increasingly important as a cause of adult meningitis in patients with head trauma and/or neurosurgical procedures [7, 17, 18]. *P. aeruginosa* is not a common pathogen in community-acquired bacterial meningitis but can be found in adult nosocomial postneurosurgical meningitis [7, 15]. In this study it was found in two cases with postneurosurgical meningitis. *N. meningitidis* has been known to be a common pathogen in community acquired bacterial meningitis [1, 7] but it is rare as a pathogen of nosocomial meningitis in adults [7], and it was also an uncommon pathogen in this study. *S. viridans* is uncommon as a causative pathogen in both community-acquired and nosocomially acquired adult bacterial meningitis [7, 19], and it was an uncommon pathogen in this study, too. In addition to the above-mentioned pathogens, the other pathogens found in this study including *A. baumannii*, *S. marcescens*, *C. diversus* and *P. mirabilis* were not common pathogens of community-acquired adult bacterial meningitis [1, 7] but can be found in meningitis of patients in postneurosurgical states [10–12, 20–22].

Removal of the colonized shunt is one of the important steps in the treatment of hydrocephalus with shunt infection [23]. Appropriate antibiotic therapy with or without shunt revision was the management strategy used for the 12 cases of mixed infection here. Despite the emergence of resistant strains in six of the 12 cases, the mortality rate of our adult bacterial meningitis patients with mixed infection was 8.3% (1/12), a figure not higher than the overall mortality rates of reported adult bacterial meningitis with either single or mixed pathogens [1, 4, 7]. Postneurosurgical meningitis in adults is usually nonfatal and has a more indolent course [10, 12]. The relatively lower mortality rate of this study may be due to the fact that most of our cases belonged to the postneurosurgical meningitis group. However, although the mortality rate was not increased by the mixed pathogens of our cases, seven of the 11 surviving cases had varying degrees of neurological sequelae.

In conclusion, head trauma and/or neurosurgical procedures with or without the placement of CNS devices have contributed greatly to the development of mixed infection in adult bacterial meningitis. Despite the complexity of implicated pathogens and the high incidence of emergence of multi-antibiotic-resistant strains that may result in a therapeutic challenge in the choice of initial antibiotics, the patients may survive with appropriate antibiotic therapy and adequate surgical intervention. Although the case number is too small to make a statistical analysis, our study shows some evidence that although the mortality rate is not especially increased in this special CNS infectious disease, most patients have difficulty in completely recuperating and neurological sequelae commonly occur.

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