Adult Acinetobacter Meningitis and Its Comparison with Non-acinetobacter Gram-negative Bacterial Meningitis

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Abstract- Between January 1999 and December 2003, 81 cases of single pathogen-related culture-proven Gram-negative adult bacterial meningitis were identified at Chang Gung Memorial Hospital-Kaohsiung. Of these 81 cases, Acinetobacter infection was found in 13 cases. Clinical and laboratory data of these Acinetobacter meningitis patients were studied and were compared with those of other 68 non-Acinetobacter Gram-negative bacterial meningitis (GNBM) patients. Of the 13 implicated Acinetobacter strains, *A. baumannii* was the most common (12), and the other was *A. lwoffii* (1). Eleven of these 13 cases were due to a post-neurosurgical infection. The results of the antibiotic susceptibility test of the 13 Acinetobacter strains from cerebrospinal fluid included ceftriaxone, (1/13, 8%), ciprofloaxin (6/13, 46%), ceftazidime (6/13, 46%), cefepime (7/13, 54%), ampicillin-subtactam (7/13, 54%), imipenem (12/13, 92%) and meropenem (12/13, 92%). One strain with pan-drug resistant *A. baumannii* (PDRAB) emerged in 2003. A statistically significant difference between Acinetobacter meningitis and non-Acinetobacter GNBM included hydrocephalus and ceftazidime-resistance. A mortality rate was 30% (4/13), and 7 of the other 9 survivals had severe neurologic deficits. The emergence of Acinetobacter infections in adult post-neurosurgical infections, multiple antibiotic resistant characteristics, and the emergence of PDRAB strain remained a challenge of the initial management of this specific meningitis. Use of carbapenem, especially meropenem, could be considered as one of the initial empiric antibiotics chosen for the management of adult post-neurosurgical meningitis.

Key Words: Acinetobacter meningitis, Carbapenem, Ceftazidime resistance, Empiric antibiotic, PDRAB

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INTRODUCTION

Despite the advent of new antibiotics, adult bacterial meningitis remains a disease of high morbidity and mortality[1,2]. The treatment of bacterial meningitis is revolutionized by the advent of new antibiotics and third generation cephalosporins are the main therapeutic choice in the treatment of Gram-negative bacterial meningitis

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(GNBM)[2,3]. However, therapeutic problems continue. Of the third generation cephalosporins, ceftazidime is the main one used in the treatment of GNBM, especially in post-neurosurgical meningitis[2-4]. The emergence of *Acinetobacter (A.) species* as the implicated pathogen of adult bacterial meningitis and the emergence of pan-drug resistant *A. baumannii* (PDRAB) strain have caused a therapeutic challenge, especially in the choice of initial empiric antibiotics[4-7]. In this study, the clinical records and laboratory data of 13 adult patients with single pathogen infected Acinetobacter meningitis were analyzed and compared with those of single pathogen infected non-Acinetobacter GNBM in order to delineate the clinical characteristics of this uncommon bacterial meningitis in adults. The antibiotic susceptibility to ceftazidime of the 13 Acinetobacter strains and other 68 pathogenic strains of non-Acinetobacter GNBM was also studied.

PATIENTS AND METHODS

We retrospectively reviewed the microbiological records for cerebrospinal fluid (CSF) and medical records, using preexisting standardized forms, of adult patients with bacterial meningitis admitted to Chang Gung Memorial Hospital (CGMH)-Kaohsiung over a period of 5 years (January 1999-December 2003). During the study period, 138 cases of culture-proven adult bacterial meningitis were identified. Of these 138 cases, 127 cases were found to have a single pathogen infection including of post-neurosurgical infection (72) and spontaneous infections (55) while the other 11 cases involving polymicrobial infections. Among the 127 patients with a single pathogen infection, 13 had Acinetobacter meningitis. Of the 11 patients with mixed-bacterial meningitis, 5 had *Acinetobacter species*. In this study, the clinical characteristics, results of antimicrobial susceptibility tests and therapeutic outcome of the aforementioned 13 cases of Acinetobacter meningitis were analyzed. During the same study period, other 68 cases of single-pathogen infected non-Acinetobacter Gram-negative bacterial meningitis (GNBM) were also used for comparison.

In this study, the criteria for a definite diagnosis of adult Acinetobacter meningitis were as follows: A) age ≥17 years old; B) a positive cerebrospinal fluid (CSF) culture of *Acinetobacter species* in patients with clinical presentations of acute bacterial meningitis including fever, headache, altered consciousness and seizures; and C) at least one of the following CSF parameters: 1) a leukocyte count $>0.25\times10^9$ /L with predominant polymorphonuclear cells; 2) a CSF lactate concentration >3.5 mmol/L; 3) a glucose ratio (CSF glucose/serum glucose) <0.4 or CSF glucose concentration <2.5 mmol/L if no simultaneous blood glucose was determined.

In this study, "nosocomial meningitis" was defined as a positive bacterial infection which was not present when the patient was admitted to the hospital, or clinical evidence of infection no sooner than 7 days after admission. Otherwise, the patient was considered to have a "community-acquired meningitis". Meningitis related to head trauma as a result of skull fracture, neurosurgical procedures or any causes of skull defects was classified as a "post-neurosurgical meningitis". Otherwise, patients who did not demonstrate clearly distinctive disease characteristics or who had not undergone invasive procedures were classified as the "spontaneous meningitis". Patients were considered to have "mixed-bacterial meningitis" if at least two bacterial organisms were isolated concomitantly from CSF cultures[8].

The Acinetobacter strains cultured from these 13 patients with single pathogen infections were examined. Automatic identification system for Gram-negative rods was performed by API ID 32 GN (bioMerieux, Inc, Marcy-I'Etoile, France) to analyze the subtypes of the 13 Acinetobacter strains. Antibiotic susceptibility was tested using Kirby-Bauer disc diffusion method (BBL, Mueller-Hinton II agars; Becton Dickinson Microbiology Systems, Cockeysville, MD). The antimicrobial susceptibilities of all 13 Acinetobacter strains were also determined by means of the broth dilution method as described in National Committee Clinical Lab Standards(NCCLS) guidelines for minimum inhibitor concentrations (MICs). Ceftriaxone, ceftazidime, cefepime, imipenem, meropenem, ciprofloaxin and

ampicillin-subtactam were used for an antibiotic susceptibility test. Quality control strains are *Escherichia coli* ATCC 25922 and *Escherichia coli* ATCC 35218. Pandrugresistant *A. bauamnnii* (PDRAB) was used to describe isolates which are resistant to all antibiotics routinely tested including ampicillin-sulbactam, ceftriaxone, ceftazidime, cefepime, aztreonam, ciprofloxacin, amikacin, imepenem and meropenem[6,9]. The results of antibiotic susceptibility to ceftazidime of the causative strains of the other non-Acinetobacter GNBM were also used to compare with the results of ceftazidime susceptibility of the 13 Acinetobacter strains.

For a comparative analysis, the clinical features of these 13 adult Acinetobacter meningitis patients were compared with those of the other 68 adult patients with non-Acinetobacter GNBM. Data including gender, types of acquisition of infection, types of infection, clinical manifestations and therapeutic outcomes were analyzed using Chi-square test or Fisher's exact test. CSF WBC counts, total protein and lactate for the two groups were compared using the Wilcoxon rank sum test. The ages between the two groups and the time interval between the last neurosurgical procedure and the development of meningitis were compared using the Student's t-test and Wilcoxon rank sum test, respectively. Stepwise logistic regression was used to evaluate the relationship between clinical factors of the Acinetobacter GNBM and non-Acinetobacter GNBM cases. All analysis was conducted using SAS (1990)[10] and a p-value <0.05 was considered statistically significant.

RESULTS

The clinical and laboratory data of the13 adult patients with Acinetobacter meningitis are listed in Table 1. The 13 adult patients were 10 men and 3 women, aged from 18 to 80 years old (median = 61). Of these 13 patients, 11 had a history of neurosurgical operation. The neurosurgical operation included an extraventricular device (EVD) for spontaneous intracerebral hemorrhage (ICH)(6), traumatic ICH (1), traumatic subarachnoid hemorrhage (SAH) with skull fracture (1), and spontaneous SAH with intraventricular hemorrhage (1), and a ventriculoperitoneal (V-P) shunt for spontaneous ICH (1) and spontaneous SAH (1). Diabetes mellitus was also found in the case of a spontaneous ICH and a V-P shunt. The time lags between the last neurosurgical procedure and the diagnosis of meningitis were 1 to 30 days. Two of these 13 cases had a spontaneous Acinetobacter meningitis; one had DM, chronic renal insufficiency and urolithiasis[11] and the other had pneumonia.

The results of CSF studies included WBCs: 0.008×10^9/L to 8×10^9/L, glucose: 0.44 mmol/L to 9.26 mmol/L, total protein: 0.73 g/L to 5.2 g/L, and lactate: 1.87 mmol/L to 23.21 mmol/L. The causative pathogens of 81 patients with monomicrobial GNBM, are listed in Table 2. The pathogens included *A. baumannii* (12) and *A. lwoffii* (1). Blood cultures revealed *A. baumannii* in 2 cases . Table 3 shows the results of antibiotic susceptibility including ceftriaxone, (1/13, 8%), ciprofloaxin (6/13, 46%), ceftazidime (6/13, 46%), cefepime (7/13, 54%), ampicillin-subtactam (7/13, 54%), imipenem (12/13, 92%) and meropenem (12/13, 92%). One strain, emerged in 2003, was resistant to all the antibiotics tested except for an intermediate susceptibility to cefepime. Two strains *Escherichia coli* and *Stenotrophomonas maltophilia* isolated from non-Acinetobacter GNBM patients were resistant to ceftazidime.

Nine patients have survived and 4 patients died after intravenous (iv) antibiotics. Meropenem and imipenem were the main antibiotics used in the treatment of cefepime-resistant Acinetobacter meningitis. The PDRAB meningitis patient received a 26 days' intravenous cefepime treatment and survived after a change of EVD. Of the 4 expired patients, one had received an oxacillin therapy, whereas the other three had received a ceftazidime, cefepime, or meropenem therapy, respectively. Of the 9 survived patients, 2 had received ceftazidime, 2 cefepime, 1 imipenem and 4 meropenem with a duration between 10 and 48 days, respectively. Of the 9 survivals, 2 resumed a normal life and 7 remained in a state of unconsciousness. The comparative results between the Acinetobacter meningitis and non-Acinetobacter GNBM groups are listed in Table 1. The types of infection, and acquisition of infection, underlying conditions (non-diabetes mellitus, neurosurgical

Table 1. *Comparison of Acinetobacter and non-Acinetobacter Gram-negative bacterial meningitis*

	Acinetobacter (N = 13)	Non-A GNBM (N = 68)	OR	95% CI	P value
(1) Age at onset (mean age, years)	55.5±18.6	53.3±16.3			0.671
(2) Sex					
Male	10	49	1.29	0.32 - 5.21	1.000
Female	3	19			
(3) Acquisition of infection					
Community acquired	1	47	0.04	0.005 - 0.31	<0.0001
Nosocomial acquired	12	21			
(4) Types of infection					
Spontaneous form	2	41	0.12	0.02 - 0.58	0.003
Post-neurosurgical form	11	27			
(5) Interval between the last neurosurgical procedure and meningitis (days)	12.7±9.4	378.7±843.3	0.067		
(6) Underlying conditions					
Diabetes mellitus					
Yes	2	34	0.18	0.04 - 0.88	0.021
No	11	34			
Neurosurgical ventricular devices*					
Yes	11	12	25.67	5.03 - 131.07	<0.001
No	2	56			
(7) Clinical manifestations					
Fever					
Yes	12	63	0.95	0.10 - 8.88	1.000
No	1	5			
Altered consciousness					
Yes	7	44	0.64	0.19 - 2.11	0.536
No	6	24			
Seizures					
Yes	6	25	1.47	0.45 - 4.88	0.543
No	7	43			
Hydrocephalus					
Yes	10	14	12.85	3.11 - 53.19	0.0002
No	3	54			
Leukocytosis					
Yes	9	49	0.87	0.24 - 3.17	1.000
No	4	19			
Positive blood culture					
Yes	2	23	0.36	0.07 - 1.74	0.326
No	11	45			
Ceftazidime-resistant					
Yes	7	2	38.46	6.49 - 222.27	<0.0001
No	6	66			
(8) CSF data‡					
WBC counts (10^9/L)	0.85±2.38	25.90±100.21			0.002
Glucose level (mmol/L)	3.19±2.58	2.35± 2.95			0.102
Lactate level (mmol/dL)	9.11±7.83	15.96± 8.89			0.032
Total protein level (g/L)	1.87±1.65	5.50± 4.42			0.002
(9) Survived					
Yes	9	48	0.94	0.26 - 3.40	1.000
No	4	20			

* Ventriculoperitoneal shunt or external ventricular drainage.

‡ Not every patient had every test.

Non-A GNBM: Non-Acinetobacter Gram-negative bacterial meningitis.

CI: Confidence internal; OR: Odds ratio; CSF: Cerebrospinal fluid.

Table 2. *Causative organisms of single pathogen in patients with Gram-negative bacterial meningitis*

Organisms	Patients N = 81	Mortality (%) N = 24 (30)
Klebsiella pneumoniae	40	13 (33)
Acinetobacter spp.	13	4 (30)
Escherichia coli	8	2 (25)
Pseudomonas spp.	7	2 (29)
Enterobacter spp.	4	1 (25)
Proteus mirabilis	3	1 (33)
Salmonella	2	1 (50)
Neisseria meningitidis	1	0
Citrobacter diversus	1	0
Stenotrophomonas maltophilia	1	0
Serratia marcescens	1	0

found in 45% (5/11) of adult patients with mixed bacterial meningitis. Of the 13 Acinetobacter strains tested, *A. baumannii* was the most common, accounting for 92% (12/13) of them. This frequency of appearance of Acinetobacter infection and the different Acinetobacter subtypes in adult bacterial meningitis were consistent with the findings of other reports[1,2,5,12]. In this study, 11 (84%) patients had a neurosurgical operation as the preceding event for the development of Acinetobacter meningitis consistent with the previous reports of Acinetobacter infections[5,13-15].

The clinical presentations of these 13 Acinetobacter meningitis patients included fever, hydrocephalus, leukocytosis, altered consciousness and seizures. Although hydrocephalus showed a statistical significance between Acinetobacter meningitis and non-

Table 3. *Antimicrobial susceptibilities of the 13 isolated Acinetobacter strains*

Antimicrobial agent	Minimum inhibitor concentration (mg/dL)				Susceptible test		
	Breakpoints	Range	MIC_{50}	MIC_{90}	Susceptible	Intermediate	Resistant
Ceftriaxone	≦ 8	8 ~ > 64	64	64	1	4	8
Ceftazidime	≦ 8	0.06 ~ > 128	32	128	6	0	7
Cefepime	≦ 8	2 ~ > 16	8	>16	7	3	3
Imipenem	≦ 4	0.06 ~ > 16	0.5	2	12	0	1
Meropenem	≦ 4	0.06 ~ > 4	1	4	12	0	1
Ciprofloaxin	≦ 1	0.125 ~ > 8	2	> 8	6	1	6
Ampicillin/subtactam	≦ 8	0.125 ~ > 32	4	>32	7	2	4

devices), and clinical manifestations (hydrocephalus, ceftazidime-resistance) showed a statistical significance. The hydrocephalus (OR=11.52; 95% CI=2.07-64.10; p=0.005) and ceftazidime-resistance (OR=34.09, 95% CI=4.28-271.70, p=0.0009) also revealed a statistically significant using a stepwise logistic regression.

DISCUSSION

This study revealed that Acinetobacter meningitis accounted for 10% (13/127) of bacterial meningitis, 16% (13/81) of our Gram-negative bacterial meningitis, and 16.7% (12/72) of post-neurosurgical bacterial meningitis caused by single pathogen. Acinetobacter species were Acinetobacter GNBM, the clinical manifestations of these Acinetobacter meningitis patients were very similar to those of adult bacterial meningitis caused by other pathogens[1,2]. The final diagnosis of adult Acinetobacter meningitis can only be confirmed by the CSF cultures.

The Acinetobacter strains had a statistically significant higher incidence of ceftazidime-resistance (54%, 7/13) than non-Acinetobacter GNBM (3%, 2/68). This study also revealed that Acinetobacter strains accounted for 7 of 9 (78%) ceftazidime-resistant strains of the total GNBM. The high incidence of third-generation cephalosporin resistance among Acinetobacter strains was also compatible with the previous reports[6,12,14-18]. This study also revealed a lower susceptible rate of cef-

traixone than that of ceftazidime in the 13 tested Acinetobacter strains. The above result was similar to a previous report (25.2% to 48.6%)[12]. Although ceftriaxone is an important third generation cephalopsorin, it is not a suitable initial empiric antibiotic in the treatment of patients with a post-neurosurgical meningitis.

The Acinetobacter strains tested in this study had a high susceptibility to carbapenem. Meropenem and imipenem were the main antibiotics used in treating the cefepime-resistant Acinetobacter meningitis. The clinical study of carbapenems in the treatment of adult Acinetobacter meningitis is limited. However, 5 of the 6 (83%) patients survived after an i.v. imipenem or meropenem treatment. This finding raises a difficult situation in choosing initial empiric antibiotics in treating patients with post-neurosurgical bacterial meningitis, especially in Acinetobacter infection. Since *Acinetobacter species* accounted for a significant higher percentage of the post-neurosurgical adult bacterial meningitis, and the specific antibiotic susceptibility findings, use of carbapenem should be highly considered. The adjustment of antibiotics can be followed after an identification of the bacterial pathogen[4].

In this study, PDRAB accounted for 8% (1/13) of the implicated Acinetobacter strains. The emergence of PDRAB in Taiwan is possibly related to an increasing use of carbapenems and ciprofloxacin[6,9], resulting in a further therapeutic challenge in severe Acinetobacter CNS infections. In this study, the mortality rate was approximately 30% (4/13), and 78% of the survivals had severe neurologic deficits. The etiologies of the high morbidity rate may be complex including preceding neurosurgical events. However, the case number of this study is too small to make a therapeutic conclusion and further large-scale studies should be conducted to examine the therapeutic results of this specific CNS infection.

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