Coagulase-Negative Staphylococcal Meningitis in Adults: Clinical Characteristics and Therapeutic Outcomes

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Abstract

Background: We wanted to analyze the clinical characteristics and therapeutic outcomes of adult meningitis caused by coagulase-negative staphylococci (CoNS).

Patients and Methods: Over a period of 5 years (January 1999 to December 2003), 127 cases were identified as having adult culture-proven bacterial meningitis caused by a single pathogen. Of them, 14 cases with CoNS meningitis were enrolled, and their clinical characteristics and therapeutic outcomes were analyzed.

Results: The 14 cases (median age 37.5; range 24–77 years old) included nine men and five women. With polynerase chain reaction sequencing of bacterial 16S r-RNA, 10 of the 14 CoNS strains were identified as *Staphylococcus epidermidis* infection, and the other four belonged to *Staphylococcus haemolyticus*. All 14 cases were in a postneurosurgical state with insertion of a ventriculoperitoneal shunt, external ventricular device or intrathecal port A as their underlying conditions, and 12 of the 14 patients contracted the infection nosocomially. Fever (86%), leukocytosis (79%), hydrocephalus (50%), consciousness disturbance (36%), and seizure (7%) were the major clinical manifestations. All the involved CoNS strains showed resistance to oxacillin but retained their susceptibility to vancomycin and linezolid. All 14 CoNS strains had positive *mec*A gene detection. With the removal of neurosurgical devices and intravenous vancomycin therapy, 86% (12/14) of the patients survived.

Conclusion: CoNS meningitis accounted for 11% (14/127) of our adult bacterial meningitis. All adult CoNS meningitis patients had a disrupted barrier of the central nervous system as the underlying condition. *S. epidermidis* was the most common CoNS subtype involved. All involved CoNS strains were oxacillin resistant. The therapeutic result showed that adult CoNS meningitis had a mortality rate of 14% (2/14).

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Introduction

Coagulase-negative staphylococci (CoNS) are normal inhabitants of the human skin and mucous membranes. Patients most at risk for CoNS infection frequently have a disruption in their host defense mechanisms due to surgery, foreign body placement, or immunosuppression [1]. Because CoNS are common contaminants of cultures, the diagnostic definition of adult CoNS meningitis is different from the meningitis caused by other common pathogens and should be defined with more strict criteria [2]. CoNS were reported to be 52.8% of pathogens of ventriculoperitoneal (V-P) shunt infections in pediatric patients less than 8 years old [3]. However, adult CoNS meningitis has not been examined specifically in the literature [4-11]. In this study, we analyzed the clinical and laboratory characteristics, and therapeutic outcomes of 14 adult patients with CoNS meningitis.

Patients and Methods

We retrospectively reviewed the microbiological records for cerebrospinal fluid (CSF) and the medical records, using preexisting standardized forms, of adult patients (more than 17 years old) with bacterial meningitis admitted to Chang Gung Memorial Hospital (CGMH)-Kaohsiung over a period of 5 years (January 1999 to December 2003). CGMH-Kaohsiung, the largest medical center in southern Taiwan, is a 2,482-bed acute-care teaching hospital, which provides both primary and tertiary referral care. In this study, a definite diagnosis of adult CoNS bacterial meningitis fulfilled the following three criteria (A–C) completely: A)

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Table 1
Causative organisms of postneurosugical patients with bacterial meningitis caused by a single pathogen (January 1999 to December 2003).

Organism	Patients N=72	Mortality (%) N=17 (24)
Coagulase-negative staphylococci		
Staphylococcus epidermidis	10	2 (20)
Staphylococcus haemolyticus	4	0
Staphylococcus aureus	13	5 (38)
Acinetobacter		
Acinetobacter baumannii	10	3 (30)
Acinetobacter lwoffii	1	0
Klebsiella pneumoniae	8	1 (12)
Escherichia coli	6	1 (17)
Pseudomonas aeruginosa	5	2 (40)
Enterobacter		
Enterobacter cloacae	3	1 (33)
Enterobacter aerogenes	1	0
Streptococcus pneumoniae	2	1 (50)
Corynebacterium	2	0
Enterococcus	1	1 (100)
Group A streptococci	1	0
Non-A, non-B, non-D streptococci	1	0
Proteus mirabilis	1	0
Serratia marcescens	1	0
Citrobacter diversus	1	0
Stenotrophomonas maltophilia	1	0

positive CoNS cultures in at least two separate CSF studies or positive CoNS culture from the tip of an indwelling neurosurgical device [2]; B) patients with clinical presentations of acute bacterial meningitis, including fever, consciousness disturbance, seizures, or signs of meningeal irritation; C) at least one of the following parameters of purulent CSF inflammation: 1) a leukocyte count of > $0.25x10^9$/l with predominantly polymorphonuclear cells; 2) a lactate concentration of > 3.5 mmol/l; 3) a glucose ratio (CSF glucose/serum glucose) of < 0.4; or glucose concentration < 2.5 mmol/l if no simultaneous blood glucose concentration was determined. A blood culture was considered positive only when multiple blood cultures grew CoNS.

In this study, nosocomially-acquired meningitis was defined as a positive bacterial infection not present when the patient was first admitted to the hospital, or clinical evidence of infection no sooner than 48 h after admission. Meningitis related to traumatic skull fractures, neurosurgical procedures or any causes of skull defects were classified as a postneurosurgical form. Patients were considered to have mixed bacterial meningitis if at least two bacterial organisms were isolated concomitantly from the CSF culture [12].

The CoNS strains cultured from the patients with single pathogen infection were examined for subtype identification and antimicrobial susceptibility. API STAPH (bioMérieux Vitek, Inc., Hazelwood, MO, USA) was used for initial subtype identification, and the results were further confirmed by PCR sequencing of bacterial 16S r-RNA [13]. Antibiotic susceptibility was determined by the Kirby-Bauer disc diffusion method (BBL Mueller-Hinton II agars; Becton Dickinson Microbiology Systems, Cockeysville, MD, USA). Penicillin G, oxacillin, vancomycin, and linezolid were used for antibiotic susceptibility tests. PCR for *mec*A gene detection was also carried out as described by *Kampf* et al. [14].

For analysis, the clinical features of adult CoNS meningitis patients were compared with those of other adult patients with non-CoNS post-neurosurgical meningitis. Data including gender, type of acquisition of infection, type of infection, underlying conditions, clinical manifestations, and therapeutic outcomes were analyzed by means of χ^2 test or Fisher's exact test. The age and interval between the last surgical procedure and the development of meningitis, CSF data of WBC counts, glucose, total proteins and lactate for the two patient groups were compared using the Wilcoxon rank sum test. Multiple logistic regression analysis was used to evaluate the relationship between variables and the two patient groups adjusted for other potential confounding factors. Variables with a cell count of zero were eliminated for logistic analysis, and only variables with statistical significance ($p < 0.05$) were included in the final model. All of the analysis was conducted using SAS (1990) [15].

Table 2
Antimicrobial susceptibilities of the coagulase-negative staphylococci isolates.

Antimicrobial agent	Minimum inhibitory concentrations (mg/dl)			
	Range	MIC_{50}	MIC_{90}	Breakpoint
Penicillin G	≥ 16	≥ 16	≥ 16	≤ 0.12
Oxacillin	≥ 8	≥ 8	≥ 8	≤ 2
Vancomycin	≤ 0.5–2	2	2	≤ 4
Linezolid	0.125–2	1	1	≤ 4

Results

During the study period, 138 adult cases of culture-proven bacterial meningitis were identified. Of these 138 cases, 127 cases were found to have single pathogen infection, and the other 11 cases involved mixed infections. Among the 127 cases of adult meningitis with single pathogen infection, 72 had postneurosurgical states as the underlying condition. Of these 72 cases, 14 were caused by CoNS infection, and the other 58 had non-CoNS meningitis. Of the 11 cases with polymicrobial infection, three involved CoNS.

The implicated pathogens of our adult bacterial meningitis caused by single microbial infection are listed in table 1. Of the 14 CoNS strains cultured from CSF, ten were identified as *Staphylococcus epidermidis*, and the other four were *Staphylococcus haemolyticus*. Positive blood cultures were found in two cases, and they all grew *S. epidermidis*. The results of antibiotic susceptibility tests for the 14 CoNS strains are shown in table 2. All 14 strains showed resistance to oxacillin but retained their susceptibility to vancomycin and linezolid. All 14 CoNS strains showed positive for *mec*A gene detection.

The clinical characteristics, CSF data and the result of comparative studies of the 14 adult CoNS meningitis patients are in table 3. All 14 cases had postneurosurgical states as the underlying condition, with one having lumbar intrathecal port A for pain control and the other 13 having neurosurgical devices including a V-P shunt (n = 8) and external ventricular device (EVD) (n = 5). The patient with intrathecal port A developed meningi-

Table 3
Comparison of coagulase-negative staphylococci with non-CoNS bacterial meningitis.

	CoNS (N=14)	Non-CoNS (N=58)	P-value
(1) Age (median and range, years)	37.5 (24–77)	56.5 (19–77)	0.016[a]
(2) Gender			
Male	9	42	0.532[b]
Female	5	16	
(3) Interval between the last neurosurgical procedure and meningitis (median and range, days)	10.5 (3–180)	12 (1–3,000)	0.342[a]
(4) Underlying conditions			
Neurosurgical devices	14 (100)	32 (55)	0.001[b]
Alcoholism	2 (14)	1 (2)	0.095[b]
Systemic lupus erythematous	1 (7)	0	0.194[b]
Diabetes mellitus	0	14 (24)	0.057[b]
Malignancy	0	7 (12)	0.332[b]
Nasopharyngeal carcinoma	0	6 (10)	0.589[b]
Ear infection	0	3 (5)	1.000[b]
(5) Clinical manifestation			
Fever	12 (86)	52 (90)	0.648[b]
Leukocytosis	11 (79)	45 (78)	1.000[b]
Hydrocephalus	7 (50)	31 (53)	0.817[c]
Altered consciousness	5 (36)	31 (53)	0.234[c]
Positive blood culture	2 (14)	11 (19)	1.000[b]
Seizure	1 (7)	20 (34)	0.053[b]
CSF leaks	1 (7)	5 (9)	1.000[b]
Pneumocranium	0	6 (10)	0.589[b]
DKA/HHNK	0	3 (5)	1.000[b]
Hypotension on arrival	0	3 (5)	1.000[b]
Brain abscess	0	3 (5)	1.000[b]
Subdural empyema	0	2 (3)	1.000[b]
Spinal abscess	0	1 (2)	1.000[b]
(6) CSF data, median (range)[d]			
WBC counts (10^9/l)	0.02 (0.01–5.44)	0.56 (0.01–67.20)	0.009[a]
Glucose level (mmol/l)	3.47 (0.55–4.49)	2.37 (0–12.95)	0.022[a]
Total protein level (g/l)	0.29 (0.06–2.24)	2.03 (0.24–16.05)	< 0.001[a]
Lactate level (mmol/dl)	4.40 (1.65–9.02)	8.86 (2.20–23.21)	0.049[a]
(7) Survived	12 (86)	43 (74)	0.495[b]

Data are number (%) of patients, unless otherwise indicated; [a] Wilcoxon rank sum test; [b] Fisher's exact test; [c] χ^2 test, [d] not all patients were tested

tis about 180 days after the procedure, while the other 13 cases experienced a time lag of 3 to 24 days between the neurosurgical procedures and the development of meningitis. Fever, leukocytosis, hydrocephalus, and consciousness disturbances were the common clinical manifestations of these 14 cases. CSF studies revealed leukocytosis, decreased glucose levels and elevated total protein and lactate levels. Statistical analysis showed that the following factors were of statistical significance: age at onset of infection, neurosurgical devices and CSF data (white cell count, glucose level, total protein and lactate level). The above-mentioned significant variables were used in multiple logistic regression analysis, and the CSF data were logarithmically transformed to improve normality. The result showed that only the CSF total protein level ($p = 0.007$) was an independent factor of the status of adult CoNS meningitis.

With intravenous vancomycin treatment (2 g/d, median 15.5 d, range 7–42 d) and removal of the artificial apparatus, 12 patients survived and two died. Of the two patients who died, the time intervals from the diagnosis of meningitis to the removal of the neurosurgical device were all 2 days, and the duration of antibiotic treatment after the removal of the neurosurgical device was 4 days and 13 days, respectively. One of the two expired patients died in septic shock, whereas the other patient died from a newly developed intracerebral hemorrhage. As for the 12 surviving patients, the median time interval from the diagnosis of meningitis to the removal of neurosurgical devices was 2 days (range 1–22 d), and the median duration of antibiotic

treatment after removal of neurosurgical devices was 12.5 days (6 d–38 d). Of the 12 surviving patients, eight resumed a normal life, two had wheel-chair bound activity and two were in a state of consciousness disturbance.

Discussion

This study revealed that CoNS meningitis accounted for 11% (14/127) of our adult bacterial meningitis and 19.4% (14/72) of our adult postneurosurgical bacterial meningitis caused by a single pathogen. CoNS were also involved in 27% (3/11) of our adult patients with mixed bacterial meningitis. Of the 14 cultured CoNS strains, *S. epidermidis* was the most common subtype, accounting for 71% (10/14), and the other subtype, *S. haemolyticus*, accounted for 29% (4/14). The frequency of appearance of different subtypes of CoNS in bacterial meningitis is consistent with the findings of other reports with *S. epidermidis* as the most commonly implicated subtype [5–11].

All 14 cases had a postneurosurgical state with insertion of neurosurgical devices as the underlying condition, and 86% (12 of the 14) of them contracted meningitis nosocomially. These findings are consistent with the reported pathogenesis of CoNS infections [1, 16]. Compared with the clinical features of adult patients with non-CoNS meningitis, adult patients with CoNS meningitis had a relatively lower CSF total protein level. However, the clinical and statistical characteristics, as shown in table 3, of these 14 adult CoNS meningitis patients were not unique and can be found in bacterial meningitis caused by other pathogens. The final diagnosis can only be confirmed by positive CSF cultures. Therefore, in an adult patient with fever and delayed recovery of consciousness after a neurosurgical procedure, the presence of central nervous system (CNS) infection, including CoNS meningitis, should be taken into consideration.

In this study, all 14 CoNS strains were oxacillin-resistant and had positive detection for the *mec*A gene. The high incidence of oxacillin-resistant CoNS found in this study is consistent with the findings of rapid development of oxacillin-resistant CoNS strains as reported from Taiwan and other countries [17–19]. The increased incidence of oxacillin-resistant CoNS strains has resulted in therapeutic challenges, especially when dealing with CNS infections. Vancomycin was the main antibiotic used in the treatment of these 14 adult CoNS meningitis cases. Usually, vancomycin does not significantly penetrate into the CSF in the absence of meningeal inflammation, but when meningitis develops, CSF penetration can be enhanced to a moderate extent [20]. There has been limited clinical study on vancomycin used in the treatment of adult CoNS meningitis. However, 12 of the 14 patients in our study survived with intravenous administration of vancomycin therapy. This mortality rate (14%, 2/14) of adult CoNS meningitis was lower than the mortality rate of our overall adult bacterial meningitis (34%–40%) [21]. There have been guidelines published for the management of intravascular catheter-related CoNS infections [22], but there are still no data supporting the total dosage and duration of intravenous vancomycin therapy for adult CoNS meningitis patients with insertion of neurosurgical devices. The result of this study may suggest that removal of infected neurosurgical devices plus at least a 1-week course of intravenous vancomycin therapy are essential for the treatment of adult CoNS meningitis. However, the case number used in this study is small, and further large-scale studies are needed to delineate the therapeutic strategy.

In conclusion, this study revealed the following clinical and laboratory characteristics of adult CoNS meningitis: 1) all patients had postneurosurgical conditions with neurosurgical device insertion; 2) 86% of the patients contracted the infection nosocomially; 3) *S. epidermidis* was the most common subtype, followed by *S. haemolyticus*; 4) all implicated CoNS strains tested positive for *mec*A detection and were oxacillin resistant, but retained their susceptibility to vancomycin and linezolid. Presently, vancomycin is the drug of choice in the treatment of this specific CNS infection.

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