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Case report

Anaerobic bacterial meningitis in adults

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ABSTRACT

Anaerobic infection is a very uncommon condition in adult bacterial meningitis (ABM), and its clinical characteristics have yet to be clarified. We enrolled 540 patients with culture-proven bacterial meningitis during a study period of 30 years (1986–2015), of whom 13 (2.4%) had anaerobic infections. These 13 patients were eight men and five women, aged 22–77 years. Among them, 53.8% (7/13) had a postneurosurgical state as the preceding event, and 79.6% (10/13) had underlying medical conditions including diabetes mellitus, malignancy, liver cirrhosis, cerebral infarct and alcoholism. Nosocomial and mixed infections were found in 15.5% (2/13) and 46.1% (6/13) of the patients, respectively. A total of 14 anaerobic strains were isolated from cerebrospinal fluid specimens, including nine Gram-negative (G(−)) strains: *Fusobacterium nucleatum* (3), *Prevotella* species (3) and *Bacteroides fragilis* (3), and five Gram-positive (G(+)) strains: *Propionibacterium acnes* (3) and *Peptostreptococcus micros* (also known as *Parvimonas micra*) (2). All of the implicated G(+) anaerobic bacteria were susceptible to penicillin, and no multiple drug-resistant strains were found among the implicated G(−) anaerobic bacteria. Despite treatment, 30.8% (4/13) of the patients died. Of the nine survivors, 22.2% (2/9) had a full recovery, while the other 77.8% (7/9) had varying degrees of neurological deficits. Compared with the good outcome group (n = 6, modified Rankin scale (mRS) scores: 0–2), the poor outcome group (n = 7, mRS scores ≧3) had higher incidence of seizure. These results may offer a preliminary view of the clinical characteristics of anaerobic ABM.

1. Introduction

Adult bacterial meningitis (ABM) is a serious infectious disease with high rates of mortality and morbidity [1,2]. ABM caused by anaerobic bacteria infection is a rare condition and is often overlooked or under-diagnosed [2–4]. Pittman et al. [4] investigated the clinical utility of routinely testing for anaerobes in cerebrospinal fluid (CSF) cultures using brucella blood agar (BBA) plates, and reported enhanced recovery from clinically significant anaerobic pathogens. Nevertheless, the clinical characteristics of anaerobic ABM have not been investigated in detail. Therefore, in this study we analyzed the clinical characteristics and therapeutic outcomes of 13 patients with anaerobic ABM collected during a study period of 30 years (1986–2015) in order to obtain a preliminary clinical view of this uncommon infectious syndrome.

2. Methods

We retrospectively reviewed the microbiological records of CSF examinations, blood cultures, laboratory data, medical records and surgical conditions of adult patients (≧18 years) with culture-proven bacterial meningitis admitted to Chang Gung Memorial Hospital (CGMH)-Kaohsiung over a period of 30 years (January 1986–December 2015). CGMH-Kaohsiung is a 2550-bed acute-care teaching hospital providing both primary and tertiary care, and it is the largest medical center in southern Taiwan. During the study period, 540 adult patients with culture-proven bacterial meningitis were identified, of whom 13 had a positive CSF cultures for anaerobic bacteria. This study was approved by the Ethics Committee of CGMH-Kaohsiung (IRB No: 201601060B0).

In this study, the criteria for a definite diagnosis of bacterial meningitis were: (1) a positive CSF culture for bacterial pathogen (s); (2) clinical features of meningitis including fever, altered consciousness, seizures, acute hydrocephalus and signs of meningeal irritation; and (3) purulent CSF features, with at least one of the following: pleocytosis with leukocyte count >0.25×10^9/l and

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predominant polymorphonuclear cells, lactate concentration >3.5 mmol/l, glucose ratio (CSF glucose/serum glucose) < 0.4 or CSF glucose level <2.5 mmol/l if no simultaneous blood glucose level was determined [1,2]. During the study period, anaerobic cultures of CSF were not routinely performed, but if requested, two plates of CDC Anaerobe 5% sheep blood agar (Becton Dickinson Microbiology Systems Sparks, MD) and a plate of CDC Anaerobe 5% sheep blood with PEA (Becton Dickinson Microbiology Systems Sparks, MD) were included for cultures of CSF specimens. These plates were incubated in an anaerobic chamber at 35 °C for 48 h prior to being examined, and the anaerobic media were held for a total of 5 days to observe growth. From January 1986 to May 2013, when anaerobes were suspected, the following steps were performed: aerotolerance test, Gram staining, in-house biochemical tests using a RapID ANA II system (Thermo Fisher Scientific Lenexa, KS). The identification of anaerobes from June 2013 to December 2015 was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik, Bremen, Germany) [5].

In this study, the patients were considered to have "mixed bacterial meningitis" if at least two bacterial organisms were isolated from the initial CSF culture [2,6]. The patients who developed meningitis related to head trauma with skull fractures or neurosurgical procedures were classified as having "postneurosurgical" meningitis, and the patients who demonstrated no clear distinctive disease characteristics and who had not undergone any invasive procedures were classified as having "spontaneous" meningitis [2]. A "nosocomial" infection was defined as a positive bacterial infection not present when the patient was admitted to the hospital, clinical evidence of an infection no sooner than 48 h after admission, or clinical evidence of meningitis within a short period of time (usually within 1 month after discharge from the hospital where the patient had received an invasive procedure, especially a neurosurgical procedure) [1,2]. Otherwise, the patients were considered to have a "community-acquired" infection.

The initial consciousness level of the patients with ABM was classified into two groups: normal consciousness (Glasgow coma scale (GCS) score = 15) and altered consciousness (GCS score <15). "Bacteremia" was defined as multiple blood cultures growing the same bacterial pathogen. The intravenous administration of penicillin G or vancomycin with a third-generation cephalosporin (ceftriaxone, ceftazidime) were the initial empiric antibiotics used to treat adult patients with clinical evidence of bacterial meningitis. Further antibiotic treatment was then adjusted according to the results of pathogen identification and antibiotic susceptibility tests. Antibiotic susceptibility of isolated pathogens was routinely tested using the Kirby-Bauer diffusion method (BBL, Muller-Hinton II agars; Becton Dickinson Microbiology Systems, Cockeyville, MD). If anaerobic bacteria were identified, antimicrobial susceptibility of these isolated pathogens was tested using agar dilution test according to CLSI methodology [7]. For anaerobes, six antimicrobial agents were tested: Amoxicillin-Clauvlanate (4/2 ug/ml, 8/4 ug/ml), Ampicillin-Sulbactam (8/4 μg/ml, 16/8 μg/ml), Clindamycin (2 μg/ml, 4 μg/ml), Metronidazole (8 μg/ml, 16 μg/ml), Penicillin (0.5 μg/ml, 1 μg/ml) and Piperacillin (32 μg/ml, 64 μg/ml). Strains were grown on anaerobic blood agar plates for 48 h at 35 °C. Representative colonies were picked to sterile saline to a density equivalent to a 0.5 McFarland standard. This inoculum then was used to prepare the wells for agar dilution. Agar dilution tests were performed on Brucella agar (Creative, Taiwan) supplemented with 5% laked sheep blood, hemin, and vitamin K according to CLSI guidelines. The growth endpoints for agar dilution were determined visually with the aid of the photographic charts supplied in CLSI document M11-A7 and the interpretive categories were recorded according to information of interpretive categories and minimal inhibitory concentration correlates.

The modified Rankin scale (mRS) [8] was used for prognostic analysis, and the 17 patients were divided into two groups: good outcome (mRS score = 0–2) and poor outcome (mRS score ≥3). Data including sex, type of infection, underlying conditions, clinical manifestations, and therapeutic outcomes between these two groups were analyzed using the x^2 test. Differences in age and CSF data between the two groups were analyzed using the Student's *t*-test. Relationships among variables and the two patient groups were analyzed using multiple logistic regression analysis adjusted for other potential confounding factors. Variables with zero cell counts were eliminated from the logistic analysis, and only variables with statistical significance ($p < .05$) were included in the final model. All analyses were conducted using SPSS software version 20.0.

3. Results

During the study period, 13 ABM patients, aged 22–77 years, including five women and eight men had anaerobic infections. Their clinical and laboratory data are listed in Tables 1 and 2. All 13 patients had a medical and/or surgical condition as the underlying condition. A postneurosurgical state as the underlying condition was found in seven patients (Cases 3, 4, 7–9, 12, 13), and underlying medical conditions were found in 10 patients. The underlying medical conditions included diabetes mellitus (DM) in four patients (Cases 2, 3, 9, 11), malignancy in three patients (Cases 1, 8, 10), liver cirrhosis in three patients (Cases 8, 10, 11), cerebral ischemic infarct in two patients (Cases 6, 12) and alcoholism in two patients (Cases 10, 11). With regards to the route of infection, nosocomial infections were found in two patients (Cases 3, 7), and community-acquired infections in the other 11. The clinical presentations of these 13 anaerobic ABM patients were fever in 7 patients (Cases 2–8), altered consciousness in seven patients (Cases 3, 6, 8, 9–11, 13), concomitant brain abscess in six patients (Cases 1, 5, 6, 9–11), hydrocephalus in six patients (Cases 3, 4, 6, 7, 11, 13), seizures in five patients (Cases 1, 3, 7, 9, 11), cerebral infarction in four patients (Cases 2, 7, 9, 11), bacteremia in two patients (Cases 1, 9), septic shock in two patients (Cases 1 and 3) and ventriculitis in Case 6.

Of these 13 ABM patients with anaerobic infections, monomicrobial infections were found in seven patients (Cases 1, 2, 5, 8, 9, 12, 13), and mixed infections in the other six. Of the six patients with mixed infections, five had one anaerobic pathogen infection, and Case 6 had two anaerobic bacteria cultured from the CSF specimen. Therefore, a total of 14 anaerobic bacteria were identified (Tables 1 and 3). Of these 14 anaerobic bacteria, five were Gram positive (G(+)) strains including three *Propionibacterium acnes* strains and two *Peptostreptococcus micros* strains (also known as *Parvimonas micra* [9]) and the other nine were Gram negative (G(−)) strains (three *Bacteroides fragilis* strains, three *Fusobacterium nucleatum* strains, and three *Prevotella* spp. strains).

The results of antibiotic susceptibility of two *Bacteroides fragilis* strains, isolated from the CSF specimens of Cases 1 and 3, were not available. The results of antibiotic susceptibility tests of the other 12 anaerobic bacteria strains are listed in Table 3. All of the isolated strains of *Fusobacterium* and *Prevotella* spp. were susceptible to penicillin, while the *Bacteroides fragilis* strain was non-susceptible to penicillin but was susceptible to metronidazole. All of the five strains of G(+) anaerobic bacteria were susceptible to penicillin. With therapy, six (Cases 2, 8, 9 10, 12, 13) of the 13 patients had a good therapeutic outcome, and the other seven patients had poor outcomes. Statistical analysis of the clinical manifestations, laboratory data, and underlying conditions between the good and poor outcome groups (Table 2) revealed that the presence of seizures ($p = .002$) was significant. Of the 13 patients, four

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