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Non-cephalosporin-susceptible, glucose non-fermentative Gram-negative bacilli meningitis in post-neurosurgical adults: Clinical characteristics and therapeutic outcome

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ABSTRACT

Objective: The clinical and laboratory characteristics of non-cephalosporin-susceptible (non-CS) glucose non-fermentative Gram-negative (G(−)) infections in adults with postneurosurgical meningitis are rarely examined solely in the literature.

Methods: The data of 28 post-neurosurgical adults meningitis with glucose non-fermentative G(−) infections, collected during a study period of 5 years (2006–2010), were reviewed. The clinical and laboratory data between the non-cephalosporin-susceptible groups and the cephalosporin-susceptible groups were compared.

Results: A total of 30 G(−) strains were collected from the 28 enrolled cases. Among the implicated glucose non-fermentative G(−) strains, 18 strains, belonging to 17 cases, were non-CS. Among the 18 non-cephalosporin-susceptible strains, *Acinetobacter* spp. (39%, 7/18) was the most common, followed by *Pseudomonas* spp. (22%, 4/18), *Stenotrophomonas maltophilia* (22%, 4/18) and *Elizabethkingia meningoseptica* (11%, 2/18). With a comparative analysis, there were no significant difference between the non-cephalosporin-susceptible and cephalosporin-susceptible glucose non-fermentative G(−) groups. The clinical and laboratory data were also of no statistical significance between the fatal ($n = 4$) and non-fatal ($n = 13$) non-cephalosporin-susceptible groups.

Conclusion: Sixty percent (18/30) of implicated glucose non-fermentative G(−) strains of post-NS meningitis in adults are non-cephalosporin-susceptible. Among the non-cephalosporin-susceptible glucose non-fermentative G(−) strains, *Acinetobacter* spp., *Pseudomonas* spp., *S. maltophilia* and *E. meningoseptica* are the commonly implicated pathogens, and their emergence in this specific group of meningitis has caused a therapeutic dilemma. The clinical manifestations of non-cephalosporin-susceptible glucose non-fermentative G(−) meningitis were not unique; therefore, only bacterial culture and antimicrobial susceptibility test are the methods for identification confirmation.

1. Introduction

Gram-negative bacilli are important pathogens of nosocomial infection syndromes including post-neurosurgical meningitis [1,2]. Besides *Enterobacteriaceae* family, glucose non-fermentative Gram-negative bacilli are another important member of Gram-negative pathogen [3–5] and they often contaminate the hospital environment, medical equipments and the skin of healthcare worker, causing infections in medically-ill hospitalized patients [3–5]. *Pseudomonas* and *Acinetobacter* spp. and *Stenotrophomonas maltophilia* are the leading members of glucose non-fermentative Gram-negative pathogens [6], and they are often intrinsically resistant to commonly prescribed important antibiotics for adult bacterial meningitis management [7–9]. In clinical practice, a rapid introduction of appropriate empirical antibiotics is of prognostic significance in glucose non-fermentative Gram-negative infections including bacterial meningitis [2,10–12]. Thus far, 3rd and 4th generation cephalosporin are still the main empiric antibiotics with regards to bacterial meningitis management [11,12]; but in recent years, an emergence of Gram-negative infection with a 3rd or 4th generation cephalosporin resistance in post-neurosurgical patients has been noted gradually [9,13,14], resulting in a

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therapeutic challenge of bacterial meningitis management. Glucose non-fermentative Gram-negative infection was found to account for 31% of Gram-negative and 35–54% of post-neurosurgical Gram-negative meningitis in Taiwan [2,9]. Although large-scale studies of overall bacterial meningitis have been conducted, the study with a focus on the post-neurosurgical glucose non-fermentative Gram-negative meningitis is rarely reported solely [2,9]. For a better delineation of this specific group of adult bacterial meningitis, we analyzed the clinical characteristics and therapeutic outcome of post-neurosurgical adult bacterial meningitis patients with non-cephalosporin-susceptible glucose non-fermentative Gram-negative infection and made a clinical comparison with those of post-neurosurgical meningitis patients with cephalosporin-susceptible Gram-negative infection.

2. Methods

We retrospectively reviewed the microbiological records for cerebrospinal fluid (CSF) and medical records of patients with adult bacterial meningitis admitted to our hospital over a period of 5 years (2006–2010). Our hospital is the medical center in southern Taiwan and is a 2482-bed acute-care teaching hospital, serving as a primary and tertiary care center. In this study, the criteria for a definite diagnosis of adult bacterial meningitis were as follows [2]: (A) age ≥17 years old; (B) positive CSF culture in patients with clinical presentations of acute bacterial meningitis including fever, headache, altered consciousness and seizure; and (C) at least one of the following CSF parameters: (1) a leukocyte count > 0.25×10^9/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. The Ethics Committee of the Chang Gung Memorial Hospital has approved this study (IRB 101-0323C).

In this study, nosocomial meningitis was defined as positive bacterial infection not present on hospital admission, clinical evidence of infection no sooner than 48 h after admission, or clinical evidence of meningitis within one month after discharge from the hospital where the patient received an invasive neurosurgical procedure. Otherwise, the patient was considered as having “community-acquired” infection. Patients who developed meningitis related to head trauma with skull fractures or neurosurgical procedures were classified as “post-neurosurgical” meningitis. Otherwise, patients who demonstrated no clear distinctive disease characteristics and who had not undergone any invasive procedures were classified as “spontaneous” meningitis. “Mixed-infection” was defined as at least two bacterial organisms isolated concomitantly from initial CSF culture [15,16]. “Super-infection” in bacterial meningitis was defined as a condition wherein CSF grew new pathogen(s) during the therapeutic course of existing bacterial meningitis [17]. In this study, both mixed infection and super-infection were included in the group of “polymicrobial infection”.

Glucose non-fermentative Gram-negative bacilli was identified using standard methods [3,18] and was verified using the automated ID 32GN System (BioMerieux, Vitex, Hazelwood, MO, USA). Because of the glucose non-fermentative strains are usually intrinsically non-susceptible to ceftriaxone [9], we use the term “non-cephalosporin-susceptible glucose non-fermentative” to describe the glucose non-fermentative isolates which were non-susceptible to ceftazidime or cefepime. In this study, the intermediate and resistant strains were all considered to be non-cephalosporin-susceptible [19]. Both *S. maltophilia* and *Elizabethkingia meningoseptica* are known to have their own specific antibiotic susceptibility state [20–22]; therefore, they were also considered to be non-cephalosporin-susceptible in this study. The term “multi-drug resistant” Gram-negative pathogens was used to describe Gram-negative isolates which were non-susceptible to all the routinely tested antibiotics including amikacin, ceftriaxone, ceftazidime, cefepime, ciprofloxacin, imipenem, and meropenem, and ampicillin-sulbactam in *Acinetobacter baumannii* strains [23,24]. Glucose non-fermentative Gram-negative strains were verified using the automated ID 32GN System (BioMerieux, Inc., Durham, NC, USA). Antimicrobial susceptibility testing was performed on a clinical service basis using the dilution method, and using interpretative criteria for glucose non-fermentative Gram-negative pathogen [24,25]. In the study period, vancomycin plus a 3rd- or 4th-generation cephalosporin were the initial empiric antibiotics used in the treatment of patients with suspected bacterial meningitis, and the antimicrobial regimen was adjusted subsequently after the culture results were available.

For statistical analysis, the clinical characteristics, CSF data and therapeutic outcome between the adult post-neurosurgical patients with cephalosporin-susceptible and non-cephalosporin-susceptible glucose non-fermentative Gram-negative meningitis were compared. In addition, the clinical characteristics and laboratory data between the fatal and non-fatal cases of the non-cephalosporin-susceptible glucose non-fermentative Gram-negative patients were also analyzed. Data including gender, type of infection, clinical manifestations and therapeutic outcome were analyzed by means of Fisher’s exact test. Age, CSF white blood cell count, glucose, total protein, and lactate given for the two different comparative patient groups (non-cephalosporin-susceptible *vs.* cephalosporin-susceptible, fatal *vs.* non-fatal cases of the non-cephalosporin-susceptible glucose non-fermentative Gram-negative meningitis patients) were compared using the Mann–Whitney *U* test. A p-value of <0.05 was considered to be statistically significant.

3. Results

During the study period, a total of 99 adult bacterial meningitis cases were identified, and among them, 57 had a positive CSF culture of Gram-negative pathogens. Among the latter 57 Gram-negative meningitis cases, 39 belonged to monomicrobial infection, while the other 18, polymicrobial infection. Of the 57 Gram-negative meningitis cases, 47 cases belonged to the post-neurosurgical meningitis and the other 10, spontaneous meningitis. Of the 47 cases of post-neurosurgical Gram-negative meningitis, 29 cases had a monomicrobial infection while the other 18, a polymicrobial infection. Among the 29 cases of monomicrobial, 16 cases belonged to glucose non-fermentative Gram-negative bacilli and the other 13 belonged *Enterobacteriaceae* infections. Of the 18 cases of polymicrobial infection, 12 cases have glucose non-fermentative infection. A total of 30 glucose non-fermentative G(−) strains (Table 1) were isolated from the 28 cases with Gram-negative infection, and 18 of these 30 glucose non-fermentative Gram-negative strains, shown in Table 2, were non-cephalosporin-susceptible. The antibiograms of these 18 non-cephalosporin-susceptible glucose non-fermentative Gram-negative strains are also listed in Table 2. These 18 non-cephalosporin-susceptible glucose non-fermentative Gram-negative strains were isolated from the CSF specimens of 17 cases; 10 of them were of monomicrobial infection, while the other 7, polymicrobial infections. The *Pseudomonas aeruginosa* strain, cultured from the CSF specimen of Case 13, was initially cephalosporin-susceptible but became non-cephalosporin-susceptible during the therapeutic course.

The clinical and laboratory data, antibiotics used and therapeutic outcomes of the 17 post-neurosurgical glucose non-fermentative Gram-negative meningitis cases are shown in Table 2.