



Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case report

Clinical characteristics of *Citrobacter* meningitis in adults: High incidence in patients with a postneurosurgical state and strains not susceptible to third-generation cephalosporins

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ARTICLE INFO

Article history:

Received 22 March 2018

Accepted 4 June 2018

Available online xxxx

Keywords:

Citrobacter

Bacterial meningitis

Adults

Postneurosurgical

ABSTRACT

Adult bacterial meningitis (ABM) caused by *Citrobacter* (*C.*) infection is very uncommon and the clinical characteristics of this specific infectious syndrome have not been analyzed in the literature. The clinical characteristics of six *Citrobacter* ABM patients collected during a study period of 30 years (1986–2015) were enrolled, and they accounted for 1.1% (6/540) of our ABM patients. In this study, a total of 14 patients with *Citrobacter* ABM (six collected from our hospital and eight from the literature) were included for analysis. The 14 patients were nine men, three women and two with unknown gender, aged 31–84 years (median: 64 years), of whom 78.6% (11/14) had an underlying postneurosurgical condition and 21.4% (3/14) belonged to mixed infections. The most common clinical manifestations were fever (50%, 7/14), altered consciousness (50%, 7/14), and headache (28.6%, 4/14). These clinical presentations were neither specific nor unique; therefore, cerebrospinal fluid studies including cultures were important for the diagnostic confirmation. Of the implicated *Citrobacter* strains, *C. koseri* was the most common (57.1%, 8/14), followed by *C. freundii* (21.4%, 3/14) and *C. farmeri* (7.1%, 1/14). Of the *Citrobacter* strains collected from CSF specimens of our six *Citrobacter* ABM patients, 33.3% (2/6) and 66.7% (4/6) were not susceptible to ceftazidime or ceftriaxone, respectively, but they were all susceptible to carbapenem. The therapeutic results showed a mortality rate of 21.4% (3/14).

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1. Introduction

Citrobacter (*C.*), first designated in 1932, is a genus of Gram-negative (*G*(-)) coliform bacteria in the *Enterobacteriaceae* family [1,2]. *Citrobacter* spp. are considered to be environmental contaminants from human or animal excrement, and they mostly reside in the gastrointestinal tract of humans. Although these bacteria have a wide distribution in the environment including the hospital setting, they have rarely been reported to be opportunistic nosocomial pathogens. Clinically, *Citrobacter* infections are most commonly found in two groups of patients: neonates and those who are debilitated, aged or immunocompromised [2–5]. *Citrobacter* meningitis is usually caused by *C. koseri* infection, with most of the patients being less than two months of age [6–10]. Adult bacterial meningitis (ABM) caused by *Citrobacter* infection has rarely been described in the literature, with only a few cases being

reported [11–17]. Therefore, in this study, we analyzed the clinical and laboratory data of ABM caused by *Citrobacter* infections in order to delineate the clinical characteristics of this very uncommon infectious syndrome.

2. Methods

We retrospectively reviewed the microbiological examinations of cerebrospinal fluid (CSF) and medical records of patients with ABM admitted to Chang Gung Memorial Hospital – Kaohsiung from January 1986 to December 2015. During the 30-year study period, a total of 540 ABM patients were identified, of whom six had *Citrobacter* infections and were enrolled into this study. The Ethics Committee of Chang Gung Memorial Hospital approved this study (IRB No: 201601060B0). In addition, we also included eight cases of ABM caused by *Citrobacter* infection reported in the literature [11–17]. Therefore, a total of 14 ABM patients with *Citrobacter* infections were included in this study for analysis.

In this study, the criteria for a definite diagnosis of ABM were as follows [18,19]: (A) age \geq 17 years; (B) positive CSF culture in

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patients with a clinical presentation of acute bacterial meningitis including fever, headache, altered consciousness or seizures; and (C) at least one of the following CSF parameters: (1) a leukocyte count $> 0.25 \times 10^9/L$ with predominant polymorphonuclear cells; (2) a 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 level was available. *Citrobacter* meningitis was defined as patients with a positive CSF culture for *Citrobacter* spp.

The patients who developed meningitis related to head trauma with skull fractures or neurosurgical procedures were classified as having “postneurosurgical” meningitis, otherwise, the patients who demonstrated no clear distinctive disease characteristics and who had not undergone any invasive procedures were classified as having “spontaneous” meningitis. A “nosocomial” infection was defined as a positive bacterial infection not present when the patient was admitted to 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). Otherwise, the patients were considered to have a “community-acquired” infection.

Citrobacter spp. were isolated using blood agar plates (Nippon Becton Dickinson Company, Glencoe, USA) and chocolate agar plates (Becton Dickinson Company, Glencoe, USA), and identified using MALDI-TOF (matrix-assisted laser desorption ionization time of flight) (Bruker, Daltonik, Bremen, Germany) [20,21]. Antimicrobial susceptibility testing was performed on a clinical service basis using the dilution method, and using the interpretative criteria for *Citrobacter* pathogens [22]. The intermediate and resistant strains were all considered to be non-cephalosporin susceptible. Intravenous administration of 3rd- or 4th-generation cephalosporins (ceftriaxone, ceftazidime, cefepime) combined with vancomycin was the initial empiric antibiotics used for the treatment of ABM. Further antibiotics were administered according to the results of pathogen identification and susceptibility tests.

3. Results

Of the 540 ABM patients, six had *Citrobacter* infections (four with monomicrobial infections and two with mixed infections). The clinical and laboratory data and therapeutic outcomes of these patients are listed in Tables 1 and 2 as Cases 9–14. We also included eight adult patients with *Citrobacter* meningitis reported in the literature [11–17] for analysis (Tables 1 and 2 as Cases 1–8). Therefore, a total of 14 *Citrobacter* ABM patients were enrolled in this study. Of these 14 *Citrobacter* ABM patients, 11 had monomicrobial infections and three had mixed infections (Cases 5, 10, 12). Because the Judicial Commission of the International Committee on Systematic Bacteriology stated that the term “*C. diversus*” should be replaced by the term “*C. koseri*” in 1993 [23], we used *C. koseri* for the *C. diversus* infections reported in Cases 1, 3, 5, 9, 10, 11 and 13 for the further discussion in this study. Therefore, of the implicated *Citrobacter* spp., *C. koseri* was the most common found in eight patients, followed by *C. freundii* in five patients and *C. farmeri* in one patient.

The 14 ABM patients with *Citrobacter* infections included nine men, three women and two with unknown gender (Cases 3 and 4), aged 31–84 years (median, 64 years). Excluding Cases 4 and 8 whose underlying conditions were not mentioned in the literature, 11 of the patients had an underlying postneurosurgical condition (Cases 2, 3, 5, 6, 7, 9–14), including: traumatic or spontaneous intracerebral hemorrhage post craniectomy and removal of the hematoma in Cases 6, 9, 10, 11 and 14, removal of a brain tumor

in Cases 2 and 5, ruptured aneurysm and subarachnoid hemorrhage in Case 12, nasopharyngeal cancer post radiotherapy in Case 7, sphenoid sinusitis post debridement in Case 13, and multiple facial fractures in Case 3. In addition, underlying medical conditions were also found in two cases, with diabetes mellitus in Cases 1 and 6, and alcoholism in Case 1. The clinical presentations of Cases 3 and 4 were not mentioned in their original reports [13,14], however the known clinical presentations of the other 12 patients were fever (7), altered consciousness (7), headache (4), CSF leakage (1), otalgia and otorrhea (1), seizures (1) and hydrocephalus (1).

The results of antibiotic susceptibility testing of the implicated *Citrobacter* strains are shown in Table 2. With regards to the implicated *Citrobacter* strains of the eight patients reported in the literature (Cases 1–8), the antibiotic susceptibility data of Cases 3 and 4 were not available, however three *Citrobacter* strains from Cases 1, 2 and 5 were susceptible to chloramphenicol, two *Citrobacter* strains from Cases 7 and 8 were susceptible to ceftriaxone, and three *Citrobacter* strains from Cases 6–8 were susceptible to both meropenem and imipenem. With regards to the implicated *Citrobacter* strains of our six patients (Cases 9–14), the *Citrobacter* strains from Cases 11 and 13 were non-susceptible to ceftazidime, and the four strains from Cases 10, 11, 13 and 14 were non-susceptible to ceftriaxone. However, all six implicated *Citrobacter* strains were susceptible to carbapenem. With regards to the treatment outcomes, three patients (Cases 6, 7 and 10) died and the other 11 patients survived. The neurological condition of Cases 1–5 and 8 were not mentioned in the literature reports, while our patients (Cases 9 and 11–14) had variable neurologic deficits denoted as the modified Rankin scale scores shown in Table 2.

4. Discussion

Because *Citrobacter* spp. are very uncommon opportunistic pathogens in ABM, the clinical characteristics of this specific infectious syndrome have not previously been analyzed in the literature. Although *Citrobacter* spp. may flourish in a hospital setting, they are rarely the source of illnesses, except for infections of the urinary tract, and meningitis and sepsis in infants [2–4]. In this study, *Citrobacter* spp. accounted for only 1.1% (6/540) of the implicated pathogens of ABM in our hospital, supporting that *Citrobacter* infection is very uncommon in ABM. Our results also showed that 78.6% (11/14) of the *Citrobacter* ABM infections occurred in patients with a postneurosurgical condition, and 21.4% (3/14) of those with *Citrobacter* infections had a co-infection with other pathogens.

In this study, *C. koseri* (including cases with reported *C. diversus*) was the most common implicated *Citrobacter* strain (57.1%, 8/14), followed by *C. freundii* and *C. farmeri* in 35.7% (5/14) and 7.1% (1/14), respectively. These findings are similar to the studies on neonate or infant meningitis caused by *Citrobacter* infections [2,6–10]. Of these three implicated *Citrobacter* spp., *C. koseri* is usually seen in urinary tract and intestinal tract infections, although it has occasionally been reported to cause septicemia and central nervous system infections including meningitis and focal suppuration [24–27]. In addition to infections of the urinary tract, intestinal tract and bloodstream, *C. freundii* also causes infections in several other sterile sites including hepatobiliary and pancreatic systems [28–30]. Compared to these *Citrobacter* strains, *C. farmeri* is a very rare pathogen in human infections [2,16,31,32], and such patients usually have an underlying medical condition.

The clinical presentations of the patients with *Citrobacter* ABM included fever, altered consciousness, headache and purulent CSF profile (Table 2). These clinical and laboratory features were neither specific nor unique to *Citrobacter* ABM, and can be found

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