Clinical Features and Outcome of Community-Acquired Bacterial Meningitis in Adult Patients With Liver Cirrhosis

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Abstract: *Introduction:* This study aimed to analyze the clinical features, causative pathogens and therapeutic outcomes of bacterial meningitis in patients with liver cirrhosis. *Methods:* Adult cirrhotic patients with community-acquired bacterial meningitis were evaluated. Clinical data were collected over a 22-year period. For comparison, the clinical features and therapeutic outcomes between patients with and without liver cirrhosis were analyzed. *Results:* Liver cirrhosis accounted for 11% (25/217) of the predisposing factors. Significant statistical analysis between the 2 groups (patients with and without liver cirrhosis) included median Glasgow Coma Scale score at presentation, presence of seizure, bacteremia and septic shock. The mean duration between arrival at the emergency room and confirmed diagnosis of bacterial meningitis was 39 hours (range, 2–240 hours). Ten (10/25, 40%) were initially diagnosed with bacterial meningitis, and 6 (6/25, 24%) were initially suggested as having infection of unknown origin. In this study, *Klebsiella pneumoniae* was the most frequent causative pathogen in patients with liver cirrhosis. The overall case fatality rates for patients with and without liver cirrhosis were 38.5% (74/192) and 64% (16/25), respectively. *Conclusions:* Patients with liver cirrhosis have a more fulminant course with a higher prevalence of disturbed consciousness, bacteremia, seizure and shock. Diagnosis and effective treatment ARE often delayed, resulting in high overall mortality. When patients with liver cirrhosis develop disturbed consciousness, seizures and septicemia, immediate neuroimaging and cerebrospinal fluid studies should be undertaken to determine bacterial meningitis. Early diagnosis and treatment are essential for survival.

Key Indexing Terms: Adult community-acquired bacterial meningitis; Liver cirrhosis; Outcome. **[Am J Med Sci 2010;340(6):452–456.]**

Despite the advent of new antimicrobial drugs and modern imaging techniques, mortality and morbidity rates of adult bacterial meningitis remain high.[1–3] Delayed diagnosis and inappropriate treatment inevitably contribute to unfavorable outcomes.[4]

Patients with liver cirrhosis are at increased risk of bacterial infections.[5] To date, only a limited number of clinical research has focused specifically on bacterial meningitis in patients with liver cirrhosis,[6–8] with liver cirrhosis accounting for 3.6% to 4.8% of predisposing factors in different series.[6,9] Because of the benefits of early diagnosis and aggressive treatment, there is a need for better delineation of potential risk factors and clinical features in this specific patient group.

Hospital-based studies provide accurate information regarding diagnosis, prevalence of causative pathogens, risk factors, clinical features and causes of mortality. This study focused on the relative frequency for each bacterial pathogen, clinical features and therapeutic outcomes of adult patients with culture-proven community-acquired bacterial meningitis in a 22-year period. For comparison, the causative pathogens and therapeutic outcomes of bacterial meningitis cases with and without liver cirrhosis were also analyzed.

PATIENTS AND METHODS

The microbiologic records for cerebrospinal fluid (CSF), blood cultures, and medical records of adult patients with bacterial meningitis admitted to the Chang Gung Memorial Hospital-Kaohsiung from January 1986 to December 2007 were retrospectively reviewed using preexisting standardized forms. The 2482-bed acute-care teaching hospital is the largest medical center in southern Taiwan, providing both primary and tertiary referral care. There were 217 cases, aged 16 years and older, with culture-proven adult community-acquired bacterial meningitis during the study period. Of these, 25 adult patients had liver cirrhosis as the underlying condition on presentation.

The criteria for definite diagnosis of meningitis included positive cultures of CSF and/or blood in patients with clinical presentations of acute bacterial meningitis, in addition to at least one of the following parameters of bacterial inflammation of CSF: (1) leukocyte count $>100/\mu L$ with predominant polymorphonuclear cells in immunocompetent host or $>50/\mu L$ in immunocompromised host; (2) CSF lactate concentrations >3.5 mmol/L; (3) CSF glucose divided by blood sugar value in a ratio <0.4; or (4) CSF glucose <2.5 mmol/L if no simultaneous blood glucose was determined.[1,3,4] Diphtheroids, coagulase-negative *staphylococci* or propionibacteria isolated from CSF were considered as causative agents only if found repeatedly or if cultured from the tip of an indwelling neurosurgical devices.[1] Patients were not considered as having bacterial meningitis were those who: (1) only demonstrated positive cultures from vascular access or surgical sites but with no isolations of pathogens from CSF and (2) only demonstrated 1 positive blood culture serving to establish the diagnosis of bacteremia but with no isolation of bacterial pathogens from CSF.

Definitions used for this study for the modes of contracting bacterial meningitis were modified from the previous reports.[10] "Community-acquired bacterial meningitis" was defined as bacterial meningitis contracted outside a hospital environment. "Bacteremia" was defined as an invasion of the bloodstream by bacteria. Coagulase-negative *staphylococcus* or other common skin contaminant were considered as causative agents only if found repeatedly from blood, through a wound or infection or through a surgical procedure or injection. Bacteremia might cause no symptoms and resolve without treatment, or it might produce fever and other symptoms of infection. In some cases, bacteremia might lead to septic shock.[11,12]

The criteria for definite diagnosis of septic shock included both evidence of infection, through positive blood

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Submitted January 21, 2010; accepted in revised form April 28, 2010.

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culture, and refractory hypotension despite adequate fluid resuscitation. In adults, this was defined as systolic blood pressure <90 mm Hg or mean arterial pressure <60 mm Hg without requiring inotropic support or reduction by 40 mm Hg in systolic blood pressure from baseline. In addition to these 2 criteria, 2 or more of the following must be present: (1) heart rate >90 beats per minute; (2) body temperature <36°C or >38°C; (3) hyperventilation (high respiratory rate) >20 breaths per minute or $PaCO_2$ <32 mm Hg on blood gas; and (4) white blood cell count $<4 \times 10^9$ or $>12 \times 10^9$ cells/L.[13]

Liver cirrhosis was diagnosed according to cirrhotic features identified from abdominal ultrasonography and/or computed tomography or surgical findings associated with both esophageal/cardiac varices on panendoscopy and abnormal liver biochemical test results.[14] Patients with liver cirrhosis were classified into Child's class A, B and C groups. Alcoholic liver disease was defined as liver disease in a patient who maintained a daily alcohol consumption of ≥80 g per day for at least the preceding 2 years and had at least a 2-fold increase in liver enzymes with abnormal liver ultrasonography.[15] Hepatic encephalopathy was defined as a metabolically induced, potentially reversible, functional disturbance of the brain that occurs in acute or chronic liver disease. Standardized nomenclature was proposed but standardized approach to treatment, particularly of persistent, episodic and recurrent encephalopathy associated with liver cirrhosis, was not.[16]

Antibiotic susceptibility of the pathogens was tested using the Kirby-Bauer disc diffusion method (BBL Mueller-Hinton II agar, Sparks, MD; Becton Dickinson). Leukocytosis was defined as white blood cell count $>10 \times 10^9$/L of peripheral blood. Bacteremia was defined as the isolation of bacteria in more than 1 blood culture for the same patient.

Two separate statistical analyses were performed. First, baseline clinical data, including gender, sex, other underlying conditions, clinical manifestations and laboratory data on liver cirrhosis, were analyzed by univariate logistic regression. Second, multiple logistic regression was used to evaluate the relationships between baseline clinical factors and the underlying conditions of liver cirrhosis during the study period, with adjustments for other potential confounding factors. All statistical analyses were conducted using the SAS software package, Version 9.1 (2002; SAS Statistical Institute, Cary, NC).

RESULTS

The clinical, underlying diseases and laboratory data of the 217 adult patients with community-acquired bacterial meningitis were listed in Tables 1 and 2. Among them, 25 patients had liver cirrhosis as the underlying condition, including 18 men (mean age, 50.7 years; range, 34–68 years) and 7 women (mean age, 66.1 years; range, 58–73 years). The proportion of liver cirrhosis as the predisposing factors among patients with community-acquired bacterial meningitis was 11.5% (25/217). Aside from liver cirrhosis, 64% (16/25) of the 25 patients had 1 or more underlying comorbidity of which diabetes mellitus was the most frequent and was found in 44% (11/25), followed by alcoholic liver disease, malignancy and end-stage renal disease.

The initial tentative diagnoses of the 25 patients with liver cirrhosis on presentation were meningitis (10), sepsis (6), hepatic encephalopathy (2), seizure (2), alcohol withdrawal (2), transient loss of consciousness (1), cerebral infarction (1) and cellulitis (1). The mean duration between arrival at the emergency room and confirmed diagnosis of bacterial meningitis was 39 hours (range, 2–240 hours). In contrast, 14 of the 192 patients without liver cirrhosis had delayed diagnosis at the emergency room, with initial tentative diagnosis that included metabolic encephalopathy (4), diabetic ketoacidosis (3), nasopharyngeal carcinoma combined with sepsis (2), left middle cerebral artery branch infarction (1), lung cancer with leptomeningeal metastasis (1), leukemia combined with sepsis (1), non-Hodgkin lymphoma (1) and alcohol withdrawal (1).

TABLE 1. Comparison of causative organisms between patients with and without cirrhosis in 2 study periods

	Noncirrhotic patients (N = 192)	Cirrhotic patients (N = 25)
Gram-negative bacilli		
Klebsiella pneumonia	65	19
Other gram-negative bacilli	38	3[a]
Streptococcus species	41	4[b]
Staphylococcus species	22	0
Other pathogens	26	0

[a] The causative pathogens were *Streptococcus pneumoniae* (2), viridans streptococci (1) and group B streptococci (1).

[b] The causative pathogens included *Salmonella* group B (1), *Listeria monocytogenes* (1) and *pseudomonas aeruginosa* (1).

Blood cultures were done in all these 25 cases, with positive blood cultures found in 21 patients. The organisms grown from blood cultures were identical to those from the CSF cultures. In peripheral blood studies, there was leukocytosis in 15 patients and thrombocytopenia in 19 patients. The levels of blood prothrombin time international ratio ranged from 1.02 to 2.04 (mean, 1.34); serum glutamic pyruvate transaminase, 24–185 mmol/L (mean, 82); serum glutamic oxaloacetic transaminase 15–176 mmol/L (mean, 64); ammonia, 25–140 mmol/L (mean, 82); and albumin, 1.3–3.1 mmol/L (mean, 2.3). Liver echography was performed in all of the 25 cases, 16 of which belonged to the class B group of Child, whereas the other 9 were C group.

Pathogens isolated from the CSF cultures of the 217 adult cases with community-acquired bacterial meningitis were shown in Table 1. In this study, *Klebsiella pneumoniae* was the most frequent causative pathogen in patients with liver cirrhosis, accounting for 76% (19/25). The clinical features in patients with and without liver cirrhosis were listed in Table 2. Fever, presence of seizure and septic shock and disturbed consciousness were the 4 most common clinical features in both patients with and without liver cirrhosis. Forty patients had concomitant focal suppuration of which 25 had brain abscess, 12 liver abscess and 3 both liver and brain abscess. Regarding bacterial pathogens in the 40 patients with focal suppuration, *K pneumoniae* (27) was the most frequent, followed by viridans streptococci (3) and other uncommon pathogens (10). All of the 7 patients with liver cirrhosis and bacterial meningitis concomitant with metastatic septic infection had both diabetes mellitus and *K pneumoniae* infection. Of these 7 patients, 5 had brain abscess, 1 had liver abscess, and the remaining 1 had purulent pericarditis. The overall case fatality rates for the patient groups with and without liver cirrhosis were 38.5% (74/192) and 64% (16/25), respectively. The other clinical manifestations of the 217 patients were listed in Table 2.

The sex, mean age at onset, median Glasgow Coma Scale score (GCS) on presentation, other underlying conditions, clinical features and laboratory data and mean hospital