Meningitis Due to Penicillin-Resistant Neisseria meningitidis in a 20-Year-Old Man

Ren-Jy Ben, Chih-Chien Wang, and Mong-Ling Chu

Abstract: The emergence of meningococcal strains with reduced susceptibility to penicillin has been reported in several countries during the past two decades, but not in Taiwan. We report a case of meningococcal meningitis with intermediate resistance to penicillin. A 20-year-old male soldier complained of chills, fever, and headache for 2 days, followed by drowsiness. Physical examination revealed erythema of the pharynx, stiff neck, erythematous maculopapules, and petechiae over the trunk and four limbs including palms and soles. Analysis of the cerebrospinal fluid (CSF) showed a white blood cell count of 9.06 x 10^6/L, a glucose concentration of 0.165 mmol/L, and a protein concentration of 7.85 g/L. CSF culture yielded Neisseria meningitidis, serogroup B. The minimum inhibitory concentration of penicillin was determined using an E-test (0.125 µg/mL); there was no β-lactamase production. He recovered after high-dose penicillin G treatment with six doses of 24 million units per day for 11 days. The emergence of penicillin resistance in N. meningitidis in Taiwan requires surveillance. High-dose penicillin may be successful in treating penicillin-insensitive meningococcal meningitis. Alternative treatment with third-generation cephalosporins should be considered if poor response to penicillin is encountered.

Case Report

A 20-year-old male soldier visited our hospital on July 19, 2000, with the chief complaint of chills and fever with headache for 2 days, followed by general weakness, fatigue, and drowsiness. On admission, his blood pressure was 115/62 mmHg, pulse rate was 89 per minute, respiratory rate was 19 per minute, and body temperature was 36°C. He had erythema of the pharynx, stiff neck, and positive Brudzinski’s sign and Kernig’s sign. His skin had some erythematous maculopapules and petechiae scattered over the right palm and both feet, then distributed over the trunk and four limbs including palms and soles. The hemogram showed a white blood cell count (WBC) of 25.3 x 10^9/L (neutrophils 92.2%, lymphocytes 3.1%, monocytes 4.0%), hemoglobin of 2.08 mmol/L, hematocrit of 41.3%, and platelet count of 171 x 10^9/L. Urinalysis revealed WBC of 25 to 30/high-power field (HPF), red blood cell count (RBC) of 12 to 15/HPF, and mild

Division of Infectious Diseases, Department of Medicine, Armed Forces Kaohsiung General Hospital, Kaohsiung, and Department of Pediatrics, Tri-Service General Hospital, Kaohsiung.


Reprint requests and correspondence to: Dr. Ren-Jy Ben, Department of Medicine, Armed Forces Kaohsiung General Hospital, 2 Chung-Cheng 1st Road, Kaohsiung, Taiwan.
proteinuria. The serum biochemistry showed a glucose concentration of 7.26 mmol/L (normal, 3.85–6.05 mmol/L), aspartate transaminase concentration of 53.8 U/L (8–29 U/L), alanine transaminase concentration of 103.2 U/L (4–24 U/L), uric acid concentration of 0.56 mmol/L (0.24–0.5 mmol/L), and a total protein concentration of 58 g/L (60–78 g/L). The test for hepatitis B surface antigen was positive. Abdominal sonography revealed chronic liver parenchymal disease. Chest roentgenogram was normal. Lumbar puncture was performed, and yellow and turbid cerebrospinal fluid (CSF) was obtained with an initial opening pressure of 240 mmH2O. CSF analysis showed a WBC of 9,060 x 10^6/L (92% neutrophils, 8% lymphocytes), RBC of 200 x 10^6/L, glucose concentration of 0.165 mmol/L (normal, 2.75–4.4 mmol/L), and protein concentration of 7.85 g/L (0.15–0.45 g/L). Gram stain of the CSF demonstrated intracellular gram-negative diplococci. Latex agglutination (BioMerieux, Marcy l’Etoile, France) of CSF was positive for N. meningitidis. Meningococcal meningitis was diagnosed, and empirical antibiotic therapy with penicillin G 4,000,000 units intravenously every 4 hours was given. Glycerol and dexamethasone were administered. Subsequent CSF culture yielded N. meningitidis, and serogroup B was confirmed by the Centers for Disease Control, Taiwan. Disk diffusion susceptibility test against penicillin gave an inhibition zone of 24-mm diameter. Antimicrobial susceptibility test (MicroScan, Dade International Inc., West Sacramento, CA, USA) revealed sensitivity to all cephalosporins, but resistance to gentamicin, amikacin, tetracycline, and trimethoprim/sulfamethoxazole. The MIC of penicillin was determined using the E-test (AB Biodisk, Solna, Sweden), and was 0.125 µg/mL. Susceptibility to penicillin was determined using the broth microdilution method as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [10], which demonstrated an MIC of 0.12 µg/mL. A nitrocefin-impregnated disk (Cefinase, Becton-Dickinson Microbiology Systems, Cockeysville, MD, USA) was used to detect β-lactamase production, and the result was negative. The patient’s fever resolved on the fifth hospital day, and headache was relieved on the next day. Due to clinical improvement, the antibiotic regimen with penicillin G was maintained until the 11th hospital day, followed by rifampin 600 mg orally twice a day for 2 days. Petechiae resolved within 2 weeks of hospital stay. The patient was discharged on the 15th hospital day in a stable condition. He remained well at 6 months’ follow-up.

Discussion

Penicillin has been the treatment of choice for meningococcal infections for more than 40 years [11]. Meningococcal resistance to penicillin has rarely been reported [1]. The frequency of decreased susceptibility to penicillin among meningococci ranged from 0.4% to 20% between 1985 and 1989, but by 1990, had risen to 46% of isolates from patients in Spain [12]. In the USA, the low prevalence of N. meningitidis intermediate resistant to penicillin has remained unchanged from 1991 to 1997 [7]. In Taiwan, the annual number of meningococcal meningitis cases ranged from 12 to 13 during the past 5 years [13, 14]. A clinical survey of meningococcal meningitis from 1989 to 1999 found 8 of 119 cases (7%) of bacterial meningitis were caused by N. meningitidis, all of which were susceptible to penicillin [8]. A study of the microbiologic features of adult community-acquired bacterial meningitis during the period from 1995 to 1998 in Taiwan found that N. meningitidis was identified as the causative pathogen in two of 36 cases (6%), and both isolates were susceptible to penicillin [9]. In our patient, disk diffusion susceptibility test for N. meningitidis with a 10-unit penicillin disk showed an inhibition zone of 24-mm diameter. This finding prompted us to test penicillin susceptibility by E-test, and an MIC of 0.125 µg/mL was found (tested in duplicate and confirmed by broth microdilution test in the Microbiology Research Laboratory of Tri-Service General Hospital), which is moderately resistant to penicillin. The 10-unit penicillin disk clearly discriminates between susceptible and moderately resistant strains (zone diameter < 26 mm) and was useful in screening for potential resistance to penicillin in a previous study [1]. However, another study suggested that the 2-unit penicillin disk test more readily identified penicillin-resistant meningococci than the standard 10-unit penicillin disk test [15]. When an MIC test is not available, E-test provides a useful and convenient method for detecting the MIC of penicillin for N. meningitidis. The overall E-test quantitative accuracy (within 1 log2 dilution) is 93% to 97.3%, compared with that of agar dilution testing [16, 17]. Consequently, E-test could be the method of choice for separating penicillin-sensitive strains from penicillin-resistant strains in laboratories without facilities for agar dilution techniques [17]. The test for production of β-lactamase was negative in our patient. The lack of β-lactamase activity in strains with resistance to penicillin has been previously reported [1, 4, 7]. Resistance is presumably caused by alterations in penicillin-binding proteins [7, 18]. The production of β-lactamase may be a mechanism of high-level penicillin resistance in N. meningitidis [4, 18]. However, meningococci are naturally transformable, and resistance genes may have spread horizontally to produce the genetic diversity [18]. Owing to the low prevalence of penicillin resistance and the uncertainty of the clinical relevance of intermediate penicillin resistance, continued use of penicillin for treating meningococcal infections is suggested [7]. Nevertheless, treatment failure with low-dose penicillin in meningococcal meningitis has been reported [19]. A pharmacokinetic study of pediatric patients with purulent meningitis treated with standard doses of penicillin G (250,000 units kg⁻¹ d⁻¹) found
a CSF mean peak penicillin concentration of 0.8 µg/mL, which produced adequate CSF concentrations for treatment of meningococcal meningitis [20]. Consequently, penicillin should still be regarded as the first choice in the treatment of meningococcal infection and higher doses of penicillin are essential for patients with infection by resistant strains [5]. Third-generation cephalosporins have been considered alternative treatment for meningococcal infection in areas with emergence of reduced susceptibility to penicillin [12]. Among third-generation cephalosporins and other β-lactam antibiotics, ceftriaxone was the most active in the treatment of penicillin-susceptible meningococci and meningococci with diminished susceptibility to penicillin [11]. In our patient, high-dose penicillin for the treatment of meningococcal meningitis was associated with recovery. In Taiwan, N. meningitidis is no longer uniformly susceptible to penicillin. Awareness of the emergence of penicillin resistance in N. meningitidis, and continuing surveillance of meningococci for changes in antimicrobial susceptibility patterns, is needed.

ACKNOWLEDGMENT: The authors would like to thank the staff of the Division of Bacterial Diseases, Centers for Disease Control, Department of Health, the Executive Yuan, for the identification and grouping of N. meningitidis.

References