International Journal of Infectious Diseases 50 (2016) 38–43

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Clinical and pathogenic analysis of 507 children with bacterial meningitis in Beijing, 2010–2014

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ARTICLE INFO

Article history:
Received 15 February 2016
Received in revised form 15 July 2016
Accepted 15 July 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Bacterial meningitis
Children
Pathogen
Antibiotic susceptibility

SUMMARY

Objectives: To explore the clinical characteristics and analyze the pathogens of bacterial meningitis in children.
Methods: Bacterial meningitis cases occurring from January 2010 through December 2014 at Beijing Children's Hospital were reviewed retrospectively. The records of all patients, including data on clinical features and laboratory information, were obtained and analyzed.
Results: In total, the cases of 507 pediatric patients seen over a 5-year period were analyzed; 220 of these cases were etiologically confirmed. These patients were classified into four age groups: 29 days to 1 year (n = 373, 73.6%), 1–3 years (n = 61, 12.0%), 3–6 years (n = 41, 8.1%), and >6 years (n = 32, 6.3%). The main pathogens identified in this study were *Streptococcus pneumoniae* (n = 73, 33.2%), *Escherichia coli* (n = 24, 10.9%), Enterococcus (n = 22, 10.0%), and group B Streptococcus (n = 18, 8.2%). All Gram-positive bacteria were sensitive to vancomycin and linezolid. All Gram-negative bacteria were sensitive to meropenem. The total non-susceptibility rate of *S. pneumoniae* to penicillin was 47.6% (20/42). The resistance rates to ceftriaxone, cefepime, and ceftazidime were 75% (9/12), 55.6% (5/9), and 40% (4/10), respectively.
Conclusions: The main pathogen of bacterial meningitis in this study was *S. pneumoniae*. The antibiotic resistance rates among children with bacterial meningitis are of serious concern.
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1. Introduction

Bacterial meningitis continues to be a major cause of illness and death among neonates and children throughout the world.[1] In population-based studies, the incidence of acute bacterial meningitis in China ranges from 6.95 to 22.3 cases/100 000 children < 5 years of age.[2–4] Neurological sequelae are relatively common in survivors.[5–10] Available studies have shown the main causal pathogens of bacterial meningitis to be *Neisseria meningitidis*, *Haemophilus influenzae* type b (Hib), and *Streptococcus pneumoniae*.[11–15]

The incidence of bacterial meningitis has decreased since the introduction of conjugated vaccines targeting Hib, *S. pneumoniae*, and *N. meningitidis*. The incidence of bacterial meningitis changed by −31% in the USA during the years 1998–2007, from 2.00 cases per 100 000 population in 1998–1999 to 1.38 cases per 100 000 population in 2006–2007.[14] The epidemiology of meningitis in Canada has been influenced dramatically by universal immunization programs for Hib, *N. meningitidis*, and *S. pneumoniae*.[15–17] However, the incidence of this disease and associated deaths in resource-limited countries continue to grow.[18] Accurate monitoring of the pathogen-specific estimates of the number of bacterial meningitis cases is challenging in many countries because of limited laboratory-based surveillance and the misuse

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http://dx.doi.org/10.1016/j.ijid.2016.07.010
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of antibiotics. In this study, hospital-based data on bacterial meningitis were used to describe the distribution of pathogens in order to provide a baseline for the evaluation of this severe disease in China.

2. Patients and methods

2.1. Study population

Cases of bacterial meningitis occurring in patients younger than 16 years of age at Beijing Children's Hospital from January 2010 through December 2014 were reviewed retrospectively. This tertiary care hospital is a National Children's Medical Center with 970 beds and treats more than three million outpatients and 70 000 hospitalized patients every year. The records of all patients with probable or confirmed bacterial meningitis during this 5-year period were obtained. Demographic data, underlying diseases, clinical features in the patient history, laboratory findings, treatments, and outcomes were reviewed.

2.2. Diagnosis of bacterial meningitis

Any child with a sudden onset of fever (>38.5 °C rectal or >38.0 °C axillary) and with neck stiffness, altered consciousness, or other meningeal symptoms was considered a suspected bacterial meningitis patient. A case that was laboratory-confirmed, with the identification of a bacterial pathogen (Hib, *S. pneumoniae*, meningococcus, or others) in the cerebrospinal fluid (CSF) or blood of a child with clinical symptoms consistent with bacterial meningitis, was considered a 'proven' case. A suspected case with a CSF examination showing at least one of the following was considered a 'probable' case: turbid CSF appearance, leukocytosis $>100 \times 10^6$ cells/l, and leukocytosis of $10–100 \times 10^6$ cells/l with either an elevated protein level (>100 mg/dl) or decreased glucose level (<40 mg/dl). These criteria are consistent with the World Health Organization (WHO) case definition.[19]

2.3. Sample collection

CSF samples were obtained aseptically from each participant through lumbar puncture. Up to 1 ml of CSF was collected into a sterile tube. Samples were sent immediately to the hospital laboratory for a cell count, Gram staining, and bacterial culture, as well as to measure glucose and protein levels. Twenty-four hours after incubation at 35 ± 2 °C in 5% CO_2, bacterial isolates were identified by colony morphology analysis and growth requirements. After identification, isolates of *S. pneumoniae* were subsequently stored at −80 °C until further investigation. An antibiotic susceptibility test for each isolate was performed using the disk diffusion method or broth microdilution method for the minimum inhibitory concentration (MIC) values. The results were interpreted according to the Clinical and Laboratory Standards Institute Performance Standards for Antimicrobial Susceptibility Testing.[20] *Staphylococcus aureus* isolates that were resistant to either oxacillin or cefoxitin were considered methicillin-resistant *S. aureus* (MRSA). Clinical and demographic data and the therapeutic history were collected using a standard case investigation form.

2.4. Bacterial isolates

All *S. pneumoniae* isolates were identified based on typical colony morphology, Gram staining, an optochin sensitivity test (Oxoid Company, Basingstoke, UK), and an Omni serum assay (Statens Serum Institute, Copenhagen, Denmark). All isolates were stored at −80 °C until further study.

2.5. Serotyping of S. pneumoniae

The serogroups of *S. pneumoniae* were tested using the Quellung reaction with Pneumotest kits, and the serotypes were tested with factor antisera (Statens Serum Institute). The interpretation of the serotyping depended on the capsular swelling seen under phase-contrast microscopy with an oil immersion lens (magnification, 100×), as described in the literature.[10]

2.6. Ethics statement

This study was reviewed and approved by the Ethics Committee of Beijing Children's Hospital Affiliated to Capital Medical University.

2.7. Statistical analysis

Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables within two groups were compared using the independent *t*-test for parametric data and the Mann–Whitney *U*-test for non-parametric data. *p*-Values of <0.05 were considered statistically significant. All statistical analyses were conducted using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study population

A total of 507 children were included in the study; their median age was 5 months (range 29 days to 15 years). There were 326 (64.3%) boys and 181 (35.7%) girls, giving a male to female ratio of 1.8:1. These cases were classified into four age groups: 29 days to 1 year (n = 373, 73.6%), 1–3 years (n = 61, 12.0%), 3–6 years (n = 41, 8.1%), and >6 years (n = 32, 6.3%). The number of cases diagnosed each year increased over time, especially in 2014 with 136 patients, and *S. pneumoniae* was the predominant pathogen (Figures 1 and 2). A pathogen was identified in 220 (43.4%) cases, with positive results in CSF and/or blood.

3.2. Comparison of the pathogen-positive and pathogen-negative groups

The pathogen-positive group comprised 220 (43.4%) patients who had at least one pathogenic bacterial strain identified in either CSF or blood culture. The pathogen-negative group comprised 287 cases. Patients in the latter group were generally younger than those in the pathogen-positive group (median age 208 vs. 133 days, p = 0.003). The two groups of patients did not differ significantly in sex distribution or blood white blood cell (WBC) count. With

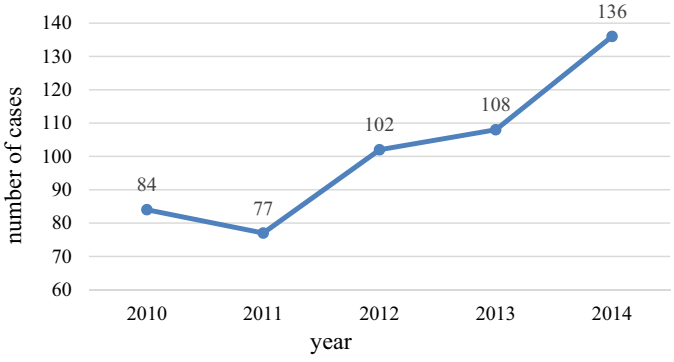

Figure 1. Number of bacterial meningitis patients diagnosed per year.

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