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Original Article

Clinical features and prognostic factors in childhood pneumococcal meningitis

Yen-Nan Chao, Nan-Chang Chiu, Fu-Yuan Huang

Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan

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Background and Purpose: Despite progress in antibiotic therapy and intensive care, childhood pneumococcal meningitis remains a devastating disease, with morbidity and mortality rates among the highest of any cause of bacterial meningitis. We conducted this study to find the factors associated with disease outcome in clinical settings.

Methods: All pediatric medical charts during the period from January 1984 to December 2003 with the diagnosis of pneumococcal meningitis were reviewed. We recorded patients' symptoms and signs, laboratory data and treatments. Outcome and neurological complications were also analyzed.

Results: In total, 40 episodes of pneumococcal meningitis from 37 patients aged 3 months to 10 years were identified. Predisposing factors were found in 13 patients (35.1%), and included recent history of head injury, immunocompromised states and cranial base anomaly. All patients had fever during illness. Patients older than 24 months of age tended to complain of nuchal rigidity (19/21, 90.5%) and those younger than 6 months of age tended to present irritability (6/7, 85.7%). The overall mortality rate was 25% (10 out of 40 episodes). The following variables were associated with mortality after statistical analysis: consciousness disturbance, shock, endotracheal tube intubation and hyponatremia (sodium <130 mEq/L) at admission (p=0.001, p<0.001, p<0.001, and p=0.012, respectively). Also, laboratory findings of less than 20/mm^3 white cell count in cerebrospinal fluid (CSF), lower CSF glucose level and CSF-to-blood glucose ratio were significantly higher in non-survivors (p=0.003, p=0.009, p=0.027). Variables associated with morbidity were seizure attack and focal neurological sign occurring hospitalization (p=0.017, p=0.017).

Conclusions: The mortality of childhood pneumococcal meningitis remains high. If a child with pneumococcal meningitis presents with consciousness disturbance, hypotension, endotracheal intubation or hyponatremia at admission, the disease mortality rate increases. CSF findings with low white cell count, low glucose level and CSF-to-blood glucose ratio are also warning signs of a bad outcome. Seizure attack and focal neurological sign are the factors associated with further neurological sequelae.

Key words: Child; Infant; Meningitis, bacterial; Mortality; Prognosis; *Streptococcus pneumoniae*

Introduction

Pneumococcal meningitis is a lethal disease in the early twenty-first century [1]. With the treatment shift from specific antiserum to systemic administration of "meningeal"-dose penicillin, the case fatality rate gradually decreased. Since the 1990's, the rate of resistance to penicillin in isolated *Streptococcus pneumoniae* has been rising and the recommended antimicrobial therapy has shifted to intravenous vancomycin, a third-generation cephalosporin, or both [2]. Dexamethasone and several adjunctive anti-inflammatory agents have been studied extensively [3]. *S. pneumoniae* is still the most common pathogen responsible for community-acquired bacterial meningitis in children in developed countries, and the associated morbidity and mortality rates are among the highest for any major pathogen [4]. We performed a retrospective study to evaluate the clinical features of childhood pneumococcal meningitis during the past twenty years in our hospital and

Corresponding author: Dr. Nan-Chang Chiu, Department of Pediatrics, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail: ncc88@ms2.mmh.org.tw

analyzed the potential factors associated with the mortality and morbidity of these children.

Methods

We reviewed the charts of all children admitted to our hospital with the final diagnosis of pneumococcal meningitis during the period from January 1984 to December 2003. Pneumococcal meningitis was defined as isolation of *S. pneumoniae* from cerebrospinal fluid (CSF) or from blood of a patient with a CSF white count >10 cells/mm^3. Patients with age less than 3 months were excluded.

Case record forms were used to collect data of patient history, symptoms and signs within 24 h after admission, complications in hospital, laboratory and microbiological data, treatment, outcome, and neurological findings at discharge and follow-up visits. Underlying predisposing factors, including asplenia, history of head trauma or neurosurgery in the past one month, anatomical or infectious otorhinolaryngeal disorders, and immunocompromised status, were recorded.

Pneumococcus resistance was defined as oxacillin disk inhibition zone >20 mm, the screening method published by the Clinical and Laboratory Standards Institute [5]. Minimal inhibitory concentration for beta-lactam susceptibility was not recorded. Urine and CSF pneumococcal antigen tests were done by latex agglutinin methods (Wellcogen® Bacterial Antigen Kit; Abbott-Murex, IL, USA). Patients were considered as having received corticosteroids (dexamethasone 0.15 mg/kg every 6 h for two or four days) only if administered before or with the first intravenous antibiotic dose.

Mortality was defined by in-hospital death in this study. Morbidity events included any neurological abnormality persisting for at least 6 months during follow-up visits. Comparison of the characteristics of different outcomes was based on Fisher's exact test and non-parametric Wilcoxon's rank-sum test. Statistical significance was defined by a p value of ≤0.05. All p values were two-sided. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (Version 10.0.7C; SPSS, Chicago, IL, USA) software package.

Results

Demographics

Forty episodes of pneumococcal meningitis were identified in 37 patients. One patient aged 4 years old had two episodes of pneumococcal meningitis within 3 months. It was found that she had common variable immunodeficiency disorder (CVID) and inner ear anomaly (Mondini's dysplasia). Another patient had three episodes of pneumococcal meningitis at the ages of three, four and five years. He experienced sensory hearing loss after the first episode, right side mastoiditis in the second episode and seizure disorder after the third episode. A series of surveys was performed, but no definite predisposing factor was discovered. Twenty seven episodes (67.5%) occurred in male patients. The mean age of patients was 37 ± 5 months old, with a range of 3 to 123 months. The age distribution is shown in Fig. 1. Eighteen episodes (45.0%) occurred below the age of 2 years and 31 episodes (77.5%) occurred below the age of 5 years.

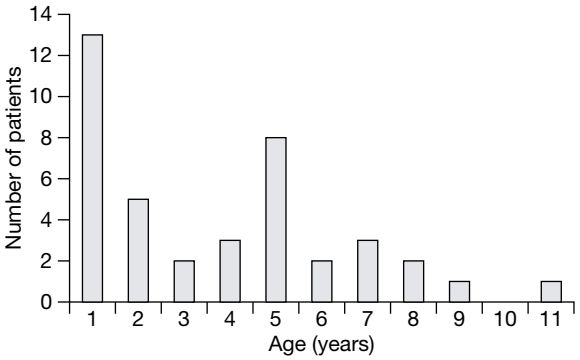

Fig. 1. Age distribution of 40 episodes of pneumococcal meningitis.

Predisposing factors and clinical pictures

Specific predisposing factors were found in 13 patients (35.1%). Six of them had history of head injury in the recent week before admission. Four of them were in immunocompromised states (acute leukemia, CVID, asplenia, T-cell immunodeficiency). Cranial base anomaly was discovered in two patients (inner ear anomaly with CSF leakage). One patient had mastoiditis.

All disease episodes had symptoms of fever (body temperature over 38.3°C). In patients older than two years, 19 of 21 episodes (90.5%) had nuchal rigidity, compared with 6 of 19 episodes (31.6%) in the younger ones. In patients younger than six months, 6 of 7 episodes (85.7%) presented irritability at admission, compared with 11 of 33 episodes (33.3%) in older patients. Twenty five episodes (62.5%) occurred in winter and spring season (October to March). None of the patients received pneumococcal vaccination. The clinical course of these episodes of meningitis is summarized in Table 1.

Table 1. Association of clinical variables with mortality in 40 children with pneumococcal meningitis

Variable	Total (n = 40) No. (%)	Survivors (n = 30) No. (%)	Non-survivors (n = 10) No. (%)	*p*
Age (months; mean ± SD)	37.0 ± 5.0	38.7 ± 6.3	31.9 ± 7.5	0.914
Male gender	27/40 (67.5)	20/30 (66.7)	7/10 (70.0)	1.00
At admission				
Fever before admission (days; mean ± SD)	2.7 ± 0.7	2.4 ± 1.5	3.8 ± 1.2	0.177
Consciousness disturbance	17/40 (42.5)	8/30 (26.7)	9/10 (90.0)	0.001
Shock	13/40 (32.5)	4/30 (13.3)	9/10 (90.0)	<0.001
Endotracheal tube intubation	10/40 (25.0)	2/30 (6.7)	8/10 (80.0)	<0.001
Hyponatremia (Na <130 mEq/L)	3/40 (7.5)	0/30 (0.0)	3/10 (30.0)	0.012[a]
During hospitalization				
Focal neurological sign	15/40 (37.5)	10/30 (33.3)	5/10 (50.0)	0.457
Seizure	16/40 (40.0)	10/30 (33.3)	6/10 (60.0)	0.159
Laboratory data				
WBC count (/mm^3; mean ± SD)	13,737 ± 1128	14,436 ± 7722	11,642 ± 7938	0.528
CRP (mg/dL; mean ± SD)	21.2 ± 2.2	20.9 ± 2.7	22.0 ± 2.7	0.476
Total CSF WBC count (mean ± SD)	816 ± 227	722 ± 160	1128 ± 859	0.06
<20/mm^3	4/39 (10.3)	1/30 (3.3)	3/9 (33.3)	0.003[a]
21-100/mm^3	8/39 (20.5)	6/30 (20.0)	2/9 (22.2)	1.00
101-1000/mm^3	18/39 (46.2)	16/30 (53.3)	2/9 (22.2)	0.14
>1000/mm^3	9/39 (23.1)	7/30 (23.3)	2/9 (22.2)	1.00
CSF protein (mg/dL; mean ± SD)	269.0 ± 30.0	242.9 ± 28.5	360.7 ± 88.0	0.156
CSF glucose (mg/dL; mean ± SD)	16.0 ± 5.0	20.0 ± 6.0	2.7 ± 1.4	0.009[a]
CSF/blood glucose ratio (mean ± SD)	0.10 ± 0.03	0.13 ± 0.04	0.02 ± 0.007	0.027[a]
Microbiology data				
Positive blood cultures	29/40 (72.5)	20/30 (66.7)	9/10 (90.0)	0.233
Positive CSF cultures	39/40 (97.5)	29/30 (96.7)	10/10 (100.0)	1.00
Positive CSF pneumococcal antigen test	17/23 (73.9)	11/17 (64.7)	6/6 (100.0)	0.144
Positive urine pneumococcal antigen test	6/18 (33.3)	5/14 (35.7)	1/4 (25.0)	1.00
Positive CSF Gram stain	22/32 (68.8)	15/24 (62.5)	7/8 (87.5)	0.380
Penicillin-resistant strain	24/40 (60.0)	16/30 (53.3)	8/10 (80.0)	0.263
Dexamethasone therapy	21/40 (52.5)	16/30 (53.3)	5/10 (50.0)	1.00

Abbreviations: SD = standard deviation; Na = sodium; CRP = C-reactive protein; CSF = cerebrospinal fluid; WBC = white blood cell
[a]$p<0.05$.

Laboratory findings

Lumbar punctures were performed in all cases and the specimens were sent for CSF cultures. Four episodes had no reliable data of CSF cytology and chemistry, due to traumatic tapping. The ratio of CSF glucose to blood glucose could only be calculated in 25 episodes. Laboratory results are summarized in Table 1.

S. pneumoniae was isolated from CSF in 39 episodes (97.5%). Twenty four pneumococcal isolates (60.0%) in this study were penicillin-resistant strains as defined by oxacillin disc screening; all were isolated after the year 1993.

Treatment

Thirty two episodes required intensive care (32/40, 80%). Dexamethasone therapy was used in 21 episodes (21/40, 52.5%). Penicillin monotherapy was used in 3 episodes. Vancomycin monotherapy was used in 5 episodes and cefotaxime monotherapy in 6 episodes. Combination therapy with penicillin or vancomycin plus a third-generation cephalosporin was used in the others.

Outcome

The overall mortality rate was 25% (10 cases). Four of them (4/10, 40%) died within 48 h after hospitalization, two died within one week, and another two died between one and two weeks after admission. The isolated pneumococcal strains in the above patients were all susceptible to the initial prescribed antibiotics. The mortality rate was 18% (2/11) in the first 10 years (1984-1993) and 27% (8/29) in the next 10 years (1994-2003), with no significant difference between these mortality rates (p=0.696).

Neurological sequelae were found in 17 episodes among the survivors (17/30, 56.7%). Late afebrile seizures were observed in 9 episodes. Hearing impairment occurred in 5 episodes. Other neurological sequelae were cerebral palsy, cranial nerve palsy and mental retardation. Neurological sequelae were found in 4 of 9 episodes in the first 10 years and 13 of 21 episodes in the latter 10 years (p=0.443).

Risk factors

Risk factors associated with death and neurological sequelae are shown in Table 1 and Table 2, respectively. Age and gender were not significantly different between survivors and non-survivors. Consciousness disturbance, shock, endotracheal tube intubation and hyponatremia (sodium <130 mEq/L) at admission occurred more frequently in non-survivors (p=0.001, p<0.001, p<0.001, and p=0.012, respectively). There was a trend towards increased mortality in cases with CSF white count less than 20/mm^3 (p=0.003). The CSF glucose level and CSF-to-blood glucose ratio were significantly lower in non-survivors (p=0.009 and p=0.027, respectively).

Among the survivors, neurological sequelae occurred more often in patients who had seizure and focal neurological sign during hospitalization (p=0.017 and p=0.017, respectively).

Discussion

Identifying a case of childhood bacterial meningitis is a truly challenging but important task. Specific predisposing factors in pneumococcal meningitis include central nervous system structural defects (skull fractures, CSF leakage, ventriculoperitoneal shunt, other structural anomalies, etc.), immunocompromised status (asplenia, sickle-cell disease, malignant disorders, etc.), and adjacent infections (mastoiditis, sinusitis, etc.). However, they are not commonly found in the disease population [6]. In our series, only one-third of patients had identifiable underlying disorders.

Childhood invasive pneumococcal diseases occur mainly before the age of five [7]. The clinical symptoms in childhood pneumococcal meningitis are not the same in all age groups. Younger patients, especially infants, present with fever, irritability or poor feeding, which are nonspecific manifestations in many diseases [8]. Since it is hard to recognize pneumococcal meningitis by symptoms in small children, rapid diagnostic

Table 2. Analysis of risk factors associated with neurological sequelae in 30 surviving children with pneumococcal meningitis

Variable	Recovery (n = 13) No. (%)	Neurological sequelae (n = 17) No. (%)	p
Age (months; mean ± SD)	46.9 ± 9.8	32.4 ± 8.1	0.263
Male gender	8/13 (61.5)	12/17 (70.6)	0.703
At admission			
Fever before admission (days; mean ± SD)	2.4 ± 0.5	2.4 ± 0.4	0.967
Consciousness disturbance	5/13 (38.5)	3/17 (17.6)	0.242
Shock	1/13 (7.7)	3/17 (17.6)	0.613
Endotracheal tube intubation	0/13 (0.0)	2/17 (11.8)	0.492
Hyponatremia (Na <130 mEq/L)	0/13 (0.0)	0/17 (0.0)	NS
During hospitalization			
Focal neurological sign	1/13 (7.7)	9/17 (52.9)	0.017[a]
Seizure	1/13 (7.7)	9/17 (52.9)	0.017[a]
CSF data			
Total CSF WBC count (mean ± SD)	545 ± 153	857 ± 256	0.742
<20/mm^3	1/13 (7.7)	0/17 (0.0)	0.433
21-100/mm^3	2/13 (15.4)	4/17 (23.5)	0.672
101-1000/mm^3	8/13 (61.5)	8/17 (47.1)	0.484
>1000/mm^3	2/13 (15.4)	5/17 (29.4)	0.427
CSF protein (mg/dL; mean ± SD)	182.6 ± 30.2	288.1 ± 41.7	0.053
CSF glucose (mg/dL; mean ± SD)	29.1 ± 11.7	13.2 ± 5.7	0.450
CSF/blood glucose ratio (mean ± SD)	0.18 ± 0.09	0.11 ± 0.04	0.884
Penicillin-resistant strain	7/13 (53.8)	9/17 (52.9)	1.000
Dexamethasone therapy	9/13 (69.2)	7/17 (41.2)	0.159

Abbreviations: SD = standard deviation; Na = sodium; CSF = cerebrospinal fluid; WBC = white blood cell

[a]p<0.05.

tools are critical in this situation, especially in patients with prior antibiotic use. Rapid diagnostic methods include detection of antigens via latex agglutination test (LAT) or immunochromatographic test, and detection of the *LytA* genes by polymerase chain reaction [9]. This study collected the results of LAT in urine and CSF specimens. CSF LAT had a higher sensitivity (73.9%) than urine LAT (33.3%). CSF Gram stain, a simple and traditional technique, has a sensitivity similar to CSF LAT (68.8%).

In this study, conscious disturbance, shock and endotracheal tube intubation at admission were associated with increased mortality rate. The major contribution to outcome is postulated to be the severity of the disease at admission, as four of our mortality cases died within 48 h after hospitalization. Since the duration of symptoms (e.g., fever) before admission was not different between survivors and non-survivors, it may be that a fulminant course caused the deaths.

A low CSF white cell count, especially less than 20/mm^3, was associated with higher mortality in this study. Studies of animals with pneumococcal meningitis showed a correlation between a lack of response of CSF leukocytes with high bacterial titers, development of intracranial complications and unfavorable outcome [10,11]. This association has also been reported in adult patients [12,13]. In the present study, a lower glucose level in CSF and hyponatremia were also predictors of a higher mortality rate.

Numerous studies have evaluated the impact of corticosteroid therapy on pediatric bacterial meningitis. It is found that steroid therapy initially decreases the incidence of hearing impairment in childhood *Haemophilus influenzae* type b meningitis [14]. But there are conflicting data regarding childhood pneumococcal meningitis. Some studies conclude that there is no benefit of dexamethasone in improving mortality or neurological outcome [15,16]. However, a population-based study from Australia concluded that with good access to health care, adjuvant steroid therapy significantly improves outcome [17]. Cochrane reviewers only suggest dexamethasone therapy as useful in childhood bacterial meningitis in industrialized countries [3]. In this study, few patients received steroid therapy, and it showed no benefit in terms of lowering the mortality and morbidity rate.

Resistance to antibiotics has complicated the management of pneumococcal meningitis in recent years. In this study, all of the penicillin-resistant strains were isolated after 1993 and the rate of penicillin resistance increased significantly afterwards, reflecting the era of emerging penicillin-non-susceptible *S. pneumoniae* in Taiwan [18,19]. As with our data, previous studies suggest that the clinical response and outcome do not differ according to whether the pneumococcal isolates are penicillin susceptible or not [20,21]. Our mortality rate lies between those of industrialized and developing countries [22]. Since antibiotics or adjunctive therapy do not effectively change the death rate of this disease, pneumococcal vaccination may be a better way to improve outcome.

This study did not record the minimal inhibitory concentrations of antibiotics and the serotypes of the isolated strains. Because the records were collected retrospectively from medical charts, these data were not available.

In conclusion, we suggest that the risk factors associated with mortality in pediatric pneumococcal meningitis include consciousness disturbance, endotracheal intubation, shock and hyponatremia at admission, as well as a low CSF glucose level and a CSF white cell count less than 20/mm^3. During hospitalization, patients who have seizure or focal neurological signs may have higher rates of neurological sequelae. Dexamethasone therapy and penicillin resistance of *S. pneumoniae* do not change morbidity and mortality rates.

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