Factors for poor prognosis of neonatal bacterial meningitis in a medical center in Northern Taiwan

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Background: Bacterial meningitis has long been a severe infectious disease in neonates, as well as a leading cause of adverse outcomes. We designed this study to know the factors for poor prognosis in neonatal bacterial meningitis.

Methods: We enrolled children aged less than 1 month who were admitted to Mackay Memorial Hospital from 1984 to 2008 and had culture-proven bacterial meningitis. The laboratory data and children's clinical features were recorded. The patients' outcomes were divided into four groups: death, having sequelae, complete recovery, and loss to follow-up. Patients with the outcomes of death and having sequelae were regarded as having a poor prognosis. Those who were lost to follow-up were excluded from the analysis of outcome. Multivariate analyses were performed to find the risk factors for poor prognosis.

Results: One hundred fifty-six neonates fulfilled the inclusion criteria. Among these, 96 were boys (61.5%) and 102 (65.4%) had concomitant bacteremia. Group B streptococci (39.1%) and Escherichia coli (20.1%) were the two leading pathogens. Excluding those who were lost to follow-up (4.5%), 22 of 149 patients (14.8%) died, 36 (24.2%) had sequelae, and 91 (61.1%) recovered completely. Cerebrospinal fluid (CSF) protein more than 500 mg/dL at admission (odds ratio (OR): 171.18 [95% confidence interval (CI): 25.6–1000]), predisposition to congenital heart disease (OR: 48.96 [95% CI: 6.06–395.64]), hearing impairment found during hospitalization (OR: 23.40 [95% CI: 3.62–151.25]), and seizure at admission or during hospitalization (OR: 10.10 [95% CI: 2.11–48.32]) were the factors predicting poor prognosis.

Conclusion: In this 25-year study of newborns with bacterial meningitis, approximately one-seventh of the patients died, while two-fifths had sequelae. Nearly two-thirds of these had concomitant bacteremia. Group B streptococci and E. coli remained the two leading pathogens...
Introduction

A recent review study on neonatal infections has reported a meningitis incidence ranging from 0.8 to 6.1 cases in every 1000 live newborns.1 Neonatal meningitis continues to be a severe disease with high morbidity, despite the fact that over the last few decades its mortality rates have reduced.2 Around 20–58% of survivors showed neurological sequelae.3–5 Early recognition of infants at risk for poor prognosis would be helpful in providing prompt management and identifying those who warrant long-term follow-up and early intervention. However, a large patient number may be required for statistical analysis to identify risk factors. Although a few neonatal bacterial meningitis studies have been reported in Taiwan,6,7 no long-period epidemiological data and prognostic factors have been published. This study reviewed the 25-year epidemiological data of culture-proven neonatal bacterial meningitis in a medical center in northern Taiwan to discover the factors for poor prognosis and assist in early detection and management of the high-risk group.

Methods

We collected the data from pediatric patients admitted to Mackay Memorial Hospital from 1984 to 2008. Only children less than 1 year of age with culture-proven bacterial meningitis were enrolled. Date of hospitalization, predisposing factors, symptoms and signs, laboratory data, pathogens in cerebrospinal fluid (CSF) and blood samples, and complications and outcomes were all collected from their medical charts.

Infections were divided into early (less than 1 week of age) and late (1 week to 1 month of age) onsets.8 Patients were further separated as preterm (gestational age <37 weeks) and term babies. Comparisons of the number having fever, predisposing factors, concomitant sepsis, pathogens, complications, and poor prognosis were made between early- and late-onset infections, as well as between preterm and term babies.

We defined predisposing factors as conditions that existed before the onset of meningitis and might worsen over the clinical course. The recorded predisposing factors included prematurity, prolonged premature rupture of membranes (PROM) (more than 24 hours),9 meconium stain in amniotic fluid, maternal antepartum hemorrhage, cesarean section (C/S), twin pregnancy, maternal fever or infection, malformation, and congenital heart disease (according to the clinical presentations and findings of physical examination, echocardiogram, electrocardiogram, chest film, and cardiac catheterization, but excluding spontaneous closure of patent ductus arteriosus and atrial septal defect). The symptoms and signs, which were listed according to the chart records, included fever, poor appetite, anterior fontanelle bulging, seizure, jitteriness, dyspnea, irritability, vomiting, diarrhea, abdominal distention, neck rigidity, cyanosis, jaundice, and sunset eyes. The complications were defined as extra medical problems that made meningitis more difficult to treat during the hospitalization period. The recorded complications included seizure, hydrocephalus, hearing impairment, subdural empyema, subdural effusion, and brain abscess.

Preterm babies were followed at our premature baby clinic until the age of 2 years, while term babies were followed at our pediatric outpatient clinic for at least 1 year. Their outcomes were divided into four groups: death, having sequelae, complete recovery, and loss to follow-up. Patients in whom the outcomes were death and having sequelae were regarded as having a poor prognosis. We defined sequelae as having consequent physical or psychological morbidities lasting for more than 6 months. Those who were lost to follow-up were excluded from analysis of outcome and mortality.

Statistical analysis

Significant differences between two different age groups and two gestational age groups were determined by χ² or Fisher’s exact test for comparison of proportions. All reported p values were two-sided and p < 0.05 was considered statistically significant.

Multivariate analysis was performed to find the risk factors for poor prognosis. Variables included in the multivariate logistic regression model assessed the net effects of each independent factor on the risk for the prognosis of neonatal bacterial meningitis. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analysis was performed using the SAS software (version 8.0; SAS Institute, Cary, NC, USA).

Results

From 1984 to 2008, 156 neonates hospitalized in Mackay Memorial Hospital met the criteria of culture-proven bacterial meningitis. Ninety-six (61.5%) neonates were boys, seven (4.5%) were lost to follow-up, and 105 (67.3%) had early-onset meningitis. The comparison between two age groups with the cut point of 1-week-old is shown in Table 1. Thirty-nine (25.0%) patients were premature babies. The comparison between them and the term babies is shown in Table 2.
Predisposing factors

Seventy-seven (49.4%) patients had predisposing factors, and 19 (12.2%) had more than one predisposing factor. Beside prematurity, 26 (16.7%) infants were born by C/S and 16 (10.3%) had congenital heart disease. No significant difference was found between either the two age groups or the preterm and term babies. However, a history of PROM (10 neonates), maternal antepartum hemorrhage (five), meconium stain in amniotic fluid (two), and twin pregnancy (two) were found exclusively only in patients less than 1 week of age.

Symptoms/signs

Fever (106 patients, 67.9%) and poor appetite (52, 33.3%) were the two leading presentations, followed by dyspnea (36, 23.1%), cyanosis (27, 17.3%), irritability (21, 13.5%), seizure (21, 13.5%), vomiting (18, 11.5%), and jaundice (18, 11.5%) (Fig. 1). Neonates younger than 7 days old had less fever \((p < 0.020)\), and both dyspnea \((p < 0.006)\) and jaundice \((p < 0.038)\) were more common in this age group. Compared to term neonates, premature babies had less fever \((p < 0.001)\).

CSF findings

Seven patients had traumatic spinal tapping or not enough CSF sample for cell count and biochemistry studies. Among the rest of the 149 patients, 31 (20.8%) CSF white blood cell (WBC) counts were regarded as normal \((< 20/mm^3)\), 21 (14.1%) CSF proteins were less than 100 mg/dL, and 30 (20.1%) CSF/blood glucose ratios were >0.67. However, only one (0.7%) patient had completely normal CSF cell count and biochemical findings.

Pathogens

Group B streptococci (GBS) (39.1%) and *Escherichia coli* (20.5%) were the two main pathogens, regardless of whether the neonates were below 1 week of age (Fig. 2). However, GBS neonatal meningitis combined with bacteremia had relatively better outcomes \([OR: 0.16 (95\% CI: 0.04–0.64)]\). No difference in the trend of the causative agents was noted in these years, nor was any significant age–pathogen relationship found. Premature infants had less GBS infection \((p < 0.011)\) than term neonates.

Concomitant bacteremia

One hundred and two (65.4%) infants had meningitis combined with bacteremia caused by the same pathogens.

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Table 1: Difference between early- and late-onset bacterial meningitis

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;1 w/o</th>
<th>≥1 w/o</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>69/36</td>
<td>27/24</td>
<td>0.124</td>
</tr>
<tr>
<td>Predisposing factors</td>
<td>51</td>
<td>26</td>
<td>0.778</td>
</tr>
<tr>
<td>Prematurity</td>
<td>31</td>
<td>8</td>
<td>0.061</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>14</td>
<td>12</td>
<td>0.109</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>11</td>
<td>5</td>
<td>0.897</td>
</tr>
<tr>
<td>Fever</td>
<td>65</td>
<td>41</td>
<td>0.020*</td>
</tr>
<tr>
<td>Combined with bacteremia</td>
<td>85</td>
<td>31</td>
<td>0.007*</td>
</tr>
<tr>
<td>Group B streptococcus infection</td>
<td>41</td>
<td>20</td>
<td>0.984</td>
</tr>
<tr>
<td><em>E. coli</em> infection</td>
<td>19</td>
<td>13</td>
<td>0.283</td>
</tr>
<tr>
<td>Gram-negative bacterial infectiona</td>
<td>55</td>
<td>28</td>
<td>0.767</td>
</tr>
<tr>
<td>Complications</td>
<td>53</td>
<td>31</td>
<td>0.226</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>9</td>
<td>11</td>
<td>0.035*</td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>38</td>
<td>20</td>
<td>0.848</td>
</tr>
<tr>
<td>Mortality</td>
<td>20</td>
<td>2</td>
<td>0.012*</td>
</tr>
</tbody>
</table>

* E. coli was excluded.
* *p* < 0.05.

Table 2: Difference between preterm and term neonates with bacterial meningitis

<table>
<thead>
<tr>
<th></th>
<th>Preterm</th>
<th>Term</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;1 w/o</td>
<td>31</td>
<td>71</td>
<td>0.033*</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>25/14</td>
<td>74/43</td>
<td>0.924</td>
</tr>
<tr>
<td>Predisposing factorsa</td>
<td>15</td>
<td>39</td>
<td>0.56</td>
</tr>
<tr>
<td>Fever</td>
<td>17</td>
<td>89</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Combined with bacteremia</td>
<td>29</td>
<td>47</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Group B streptococcus infection</td>
<td>9</td>
<td>54</td>
<td>0.011*</td>
</tr>
<tr>
<td><em>E. coli</em> infection</td>
<td>7</td>
<td>24</td>
<td>0.728</td>
</tr>
<tr>
<td>Gram-negative bacterial infection</td>
<td>31</td>
<td>64</td>
<td>0.096</td>
</tr>
<tr>
<td>Complications</td>
<td>24</td>
<td>60</td>
<td>0.164</td>
</tr>
<tr>
<td>Poor prognosisb</td>
<td>22</td>
<td>36</td>
<td>0.003*</td>
</tr>
<tr>
<td>Mortalityb</td>
<td>11</td>
<td>11</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

* *p* < 0.05.
* a Premature neonates were excluded.
* b Patients who were lost to follow-up were excluded.
Discussion

Although the meninges can be invaded by bacteria, forming on an infected skin lesion, most neonatal meningitis results from bacteremia.\(^\text{10}\) Similar to previous reports,\(^\text{6,11}\) nearly two-thirds of our neonatal meningitis patients combined with bacteremia. Transplacental hematogenous infection of maternal origin plays an important role for neonatal sepsis.\(^\text{12}\) Two-thirds of our patients had early-onset meningitis, which also indicates a strong hematogenous association.

Infants with predisposing factors are at increased risk for sepsis.\(^\text{12}\) In our study, nearly half the patients had predisposing factors and nearly two-thirds had sepsis. Although prematurity was noted as a major risk factor for late-onset GBS-related diseases by Lin et al,\(^\text{13}\) we found that premature babies had less GBS infection than term ones, which was also reported by Gaschignard et al.\(^\text{14}\)

Severe bacterial infections rarely occur in neonates without any clinical evidence of illness. Neonates having bacterial sepsis frequently show fever, jaundice, or respiratory distress,\(^\text{11}\) while abnormal body temperature (hypothermia or hyperthermia), change of activity (lethargy or irritability), and anorexia/vomiting are more common in neonatal bacterial meningitis.\(^\text{15}\) According to the study of Curtis et al,\(^\text{16}\) bulging fontanelle, neck stiffness, seizure, reduced feeding, jaundice, and fever were strongly related to meningitis in children. More symptoms and signs were mentioned as indicative of bacterial meningitis in other reports.\(^\text{17,18}\) On the other hand, clinical symptoms and signs alone may be nonspecific for diagnosing such kinds of infections.\(^\text{19}\) In our study, fever (67.9%) and poor appetite (33.3%) were the two most common presentations of neonatal bacterial meningitis. However, seizure, vomiting, jaundice, bulging fontanelle, and neck stiffness are found only in a small proportion. When a newborn is suspected to have sepsis, meningitis should also be considered and cannot be excluded by clinical presentation only.

Lumbar puncture is the mandatory procedure to diagnose meningitis, and is useful to perform in infants with clinical signs of sepsis.\(^\text{20}\) In those without meningitis, CSF cell count may be higher and glucose level may be lower in neonates than in older infants, while protein concentration may be higher in preterm than in term infants.\(^\text{21}\) Although CSF WBC count and protein concentration could be altered by a traumatic lumbar puncture, CSF sugar remains low in culture-proven bacterial meningitis. In our study, a normal CSF cell count and protein or glucose levels were found in one-fifth to one-seventh of patients. While it is compatible with the findings of Garges et al\(^\text{11}\) that no single CSF value can reliably exclude the presence of meningitis in neonates, only one of our patients showed completely normal results in all of their CSF cell count and biochemical examinations, so these parameters can still be helpful. Nonetheless, CSF culture is still the most important study for the diagnosis of neonatal bacterial meningitis.
In many countries, GBS, *E. coli*, and *Listeria monocytogenes* are the leading causative agents of meningitis occurring during the first week of life, which is mostly caused by maternal transmission.\(^5\)\(^,\)\(^14\) Occurrences after this period suggest nosocomial infection, of which *staphylococcal* species and Gram-negative rods are the main etiology.\(^3\)\(^,\)\(^4\) Distribution of the main pathogens may be different in different regions. In Iran, for example, *Klebsiella pneumoniae* and *Enterobacter* spp. were the two main pathogens of neonatal bacterial meningitis.\(^23\) In our study, GBS and *E. coli* persisted in being the two main pathogens, while *L. monocytogenes* meningitis is hardly found. A study from southern Taiwan had similar findings.\(^7\) In our long-period survey, we found no significant change of pathogen distribution, and no significant difference in Gram-negative infection between premature and term babies or early- and late-onset neonatal bacterial meningitis.

In our study, seizure, hearing impairment, and hydrocephalus are common complications of neonatal bacterial meningitis. Seizure is also an important complication of bacterial meningitis in older children.\(^24\) Coenraad et al.\(^25\) point out that sepsis and meningitis are significant risk factors for the prognosis of sensorineural hearing loss. Children with acute neurologic complications have more adverse outcomes than either those with uncomplicated meningitis or control children.\(^30\) Nearly all our patients who finally developed sequelae had complications during hospitalization.

We found CSF protein more than 500 mg/dL, predisposing to congenital heart disease, hearing impairment, and seizure to be four factors for poor prognosis in neonatal bacterial meningitis. In two retrospective studies, seizures, thrombocytopenia, high CSF protein, and low CSF glucose concentration were regarded as important prognostic factors of complications in neonatal meningitis.\(^7\)\(^,\)\(^27\) Klinger et al.\(^18\) reported that the presence of seizures, coma, use of inotropes, and leukopenia were predictors of adverse outcomes of neonatal bacterial meningitis, while, in another study, seizure, consciousness change, young age, and several CSF parameters were shown to be risk factors for predicting sequelae and death in children aged 0–18 years.\(^29\) Neonatal seizure, low birth weight, low Apgar score at 1 minute, no response after anticonvulsant therapy, abnormal cerebral ultrasound findings, abnormal neurological examination, and status epilepticus were also mentioned as factors predictive of adverse outcomes.\(^30\) According to the above reports, the presence of seizure during the course of meningitis is no doubt a significant factor related to poor prognosis in neonatal meningitis.

In conclusion, GBS and *E. coli* are the two main pathogens of neonatal bacterial meningitis, and no significant change in the trend of the latter’s causative agents has been observed in our hospital during the past 25 years. Compared with late-onset bacterial meningitis, early-onset meningitis has a higher ratio of concomitant bacteremia and mortality rate. If a newborn with bacterial meningitis predisposes to congenital heart disease, develops hearing impairment or seizure attack during hospitalization, or his/her CSF examination shows a high protein concentration, a worse outcome is more likely. By identifying high-risk infants, we could give prompt management as early as possible.

References


