Clinical Spectrum of Meningococcal Infection in Infants Younger than Six Months of Age

Hsuan-Rong Huang, MD; Hui-Ling Chen¹, DDS, MS; Shih-Ming Chu, MD

Background: *Neisseria meningitidis* is one of the most significant bacterial infections in children and adolescents. As transplacental antibodies in the circulation gradually decline, the prevalence of meningococcal disease among young infants is high, and often presents an invasive clinical manifestation. The purpose of the study was to investigate the clinical spectrum of meningococcal infection in young infants.

Methods: We retrospectively reviewed the medical charts and analyzed the clinical characteristics and outcomes of 10 infants younger than 6 months old with meningococcal disease at the Chang Gung Children’s Hospital from 1994 through 2004.

Results: A total of 10 male infants with a mean onset age of 2.9 ± 1.79 months old were enrolled. All patients presented initial symptoms of fever and decreased activity. Seizure attack was noted in six cases, and only three patients had purpuric or petechial rash. Laboratory findings reflected pyogenic infection including elevated C-reactive protein (159.1 ± 108.8 mg/L), pleocytosis (791.11 ± 660.83/µL), high protein levels (190.43 ± 157.91 g/dl) and hypoglycorrhachia (28 ± 20.89 mg/dl) in the cerebrospinal fluid. Seven cases presented meningitis; among those, *N. meningitidis* was isolated from blood in two cases. Three of the remaining patients had meningococcemia. Penicillin was the most common drug of choice; cephalosporin was the alternative. Prolonged antimicrobial therapy (range, 14 to 42 days) was prescribed in six patients complicated with subdural empyema. No deaths were documented. During long-term follow up, two patients developed mental retardation, and one of those two also had epilepsy. Both of them had lower birth body weight, altered initial conscious level, leukocytopenia and subdural empyema with encephalomalacia on brain images. One had insufficient therapy and another one was infected by a penicillin resistant strain.

Conclusions: Clinicians should be aware of meningococcal infection in young infants because the initial presentations may be difficult to distinguish from viral syndrome, and may rapidly progress to clinical deterioration. Patients with subdural empyema required prolonged courses of antimicrobial therapy. Brain images confirmed the presence of encephalomalacia which increased the risk of permanent neurologic deficit.


Key words: *Neisseria meningitidis*, subdural empyema, encephalomalacia.
Despite effective antibiotics and vaccinations, *Neisseria meningitidis* is still a leading cause of meningitis and sepsis in healthy individuals worldwide. It remains a major health problem due to epidemic outbreaks as well as endemic disease. In the United States, the incidence was estimated at around 0.8 to 1.3/100000.\(^1\) Owing to the presence of transplacental antibodies to *N. meningitidis*, the prevalence in neonates is low.\(^2\) As the antibodies gradually decline, a peak incidence is demonstrated between 1 and 6 months of life, followed by adolescents and college students living in dormitories.\(^3\) Invasive diseases are the most common among young children with the fatality rate of 10 to 20%.\(^4,5\) The purpose of this study was to investigate the clinical spectrum of meningococcal infection in young infants in order to reduce the mortality and morbidity rates.

**METHODS**

We retrospectively reviewed the medical charts for *N. meningitidis* in young infants from 1994 through 2004 at Chang Gung Children’s Hospital. Patients were identified as infants at ages younger than 6 months. Patients with meningococcal disease met the following criteria: culture positive for *N. meningitidis* in the sterile body fluid, e.g. blood, cerebrospinal fluid and synovial fluid. Demographic data and clinical manifestations were recorded. Laboratory values, microbiologic findings, and serotypes were collected. Treatment modalities, complications, and outcomes were analyzed.

**RESULTS**

Data of patient’s characteristics

A total of 10 infant boys were enrolled during the 10-year study. The mean age of onset was 2.9 ± 1.79 months. Most of them (80%) were full-term babies without systemic disease or history of previous admission. The mean birth body weight was 2797 ± 644.84 g. No identified history of contact was demonstrated, however, two patients had aboriginal ancestry.

Clinical presentations and physical findings

All of the 10 infants had initial symptoms with fever and decreased activity. Three children had altered conscious level to drowsy status, and four patients suffered from vomiting. Seizure attacks occurred in six patients, and none of the patients had focal neurological sign, such as hemi-paresis or hemi-paralysis. Only three patients had skin manifestations with purpuric or petechial rashes. One patient had septic shock resuscitated by inotropic agent and three patients required ventilator support for respiratory distress.

Laboratory values and microbiologic findings

Three patients had leukocytosis (white blood cell count more than 15000/µL) and another three patients had leukocytopenia (white blood cell count less than 5000/µL). The mean white blood cell count was 10300 ± 7484/µL. Anemia (hemoglobin less than 8 g/dl) was found in two patients, and three patients had thrombocytopenia (platelet count less than 100000/µL). The mean value of hemoglobin and platelet count was 9.02 ± 1.57 g/dl and 245500/µL, respectively. Coagulation studies were obtained in five patients on admission, and four of them had prolonged partial thromboplastin time (PTT) and prothrombin time (PT). The mean value of C-reactive protein was 159.1 ± 108.8 mg/L. Studies of cerebrospinal fluid (CSF) were obtained in all cases which disclosed pleocytosis (791.11 ± 660.83/µL), raised protein levels (190.43 ± 157.91 g/dl) and hypoglycorrachia (2.8 ± 20.89 mg/dl). *N. meningitidis* was isolated in five patients (50%) from blood cultures and seven patients (70%) from CSF cultures, respectively. Both blood cultures and CSF cultures yielded *N. meningitidis* growth in two cases (20%). Serogroups were available for five isolates. Serogroup B was isolated in three patients and serogroup W135 was categorized in another two patients. Clinical characteristics and laboratory values are shown in Table 1.

Managements and outcomes

The treatment modalities were at the discretion of the individuals attending to each admission. Penicillin was the most common drug of choice (70%). The third-generation cephalosporin was an alternative treatment regimen. According to the sensitivity test, only one was a penicillin resistant strain. Therapy was continued for 7 to 10 days in three patients with meningococcemia and 1 patient with meningitis without complications. Prolonged antibi-
Meningococcal infection in young infants

Otic treatments (range, 14 to 42 days) were prescribed in six patients complicated with subdural empyema confirmed by the results of brain echo and computed tomography (CT). One patient received craniotomy for drainage. No deaths were documented at our institution under aggressive resuscitations and appropriate antibiotics treatments. The mean hospital stay was 25.5 ± 13.05 days.

Long-term follow up
In this study, Case 1 and case 6 were diagnosed with mental retardation (20%) during long-term follow up. Case 6 was also complicated with epilepsy. In comparison with those without sequelae, both of them had low birth body weight (2050 g and 2000 g), altered initial conscious level, and leukocytopenia. In addition, they sustained subdural empyema; unlike case 6 who completed cefotaxime for 6 weeks, case 1 received insufficient therapy with aqua-penicillin for only 2 weeks. However, case 6 was infected by a penicillin resistant strain. Encephalomalacia was a concomitant finding on brain CT. Table 2 depicts the complications, treatment modalities and outcomes of the 10 infants with meningococcal infections.

DISCUSSION
The incidence of meningococcal disease is the highest during the first year of life. The pathogeneses include the gradual declined of transplacental antibodies beyond 6 months of age and immature development of self immunity. The other presumptions of victims are no nature immunity to N. menin-

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
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<tr>
<td>1</td>
<td>Meningitis</td>
<td>Subdural empyema</td>
<td>Aq-PCN for 14 days</td>
<td>Sensitivity to Aq-PCN</td>
<td>Mental retardation</td>
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<tr>
<td>2</td>
<td>Meningitis</td>
<td>Subdural empyema</td>
<td>Aq-PCN for 34 days</td>
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<td>3</td>
<td>Meningitis with Meningococcemia</td>
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<td>Aq-PCN for 26 days</td>
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<td>Aq-PCN for 7 days</td>
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<td>5</td>
<td>Meningitis with Meningococcemia</td>
<td>Subdural empyema</td>
<td>Ceftriaxone for 14 days</td>
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<td>6</td>
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<td>7</td>
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<td>Sensitivity to Aq-PCN</td>
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<td>8</td>
<td>Meningococcemia</td>
<td>Subdural empyema</td>
<td>Aq-PCN for 7 days</td>
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<td>9</td>
<td>Meningococcemia</td>
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<td>10</td>
<td>Meningitis</td>
<td>Subdural empyema</td>
<td>Aq-PCN for 42 days</td>
<td>Sensitivity to Aq-PCN</td>
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Abbreviations: Aq-PCN: aqua-penicillin.
gitidis of the mother before pregnancy or lower levels of terminal complement components that result in impaired function of phagocytosis.\textsuperscript{2,6,7} Male predominance was documented in our study which is consistent with previous estimated epidemiologic data. Although no history of contact was identified, we emphasize that thorough interrogation of each patient’s history provides essential information for a correct diagnosis. The carriage rate of nasopharyngeal colonization is 5-10\% and it is higher in crowded conditions and low socioeconomic status. The organisms are transmitted from person to person by aerosolization or direct contact with respiratory secretions, and then invade by penetration through mucosa into the bloodstream and cerebrospinal fluid.\textsuperscript{3} Individuals with underlying immune defects, such as deficiency of terminal complement components or properdin, agamma or hypogammaglobulinemia, and asplenia are at increased risks for meningococcal disease. The other predisposing factors are crowded living conditions, lower socioeconomic status, exposure to tobacco smoke, and concurrent viral infection.\textsuperscript{8,9} In addition, there is increased risk of infection in the persons who have close contact with a patient with meningococcal disease,\textsuperscript{9} and chemoprophylaxis are recommended as soon as possible for the household, daycare center or health worker who has had contact with the patient’s secretions during the 7 days prior to the onset of symptoms.\textsuperscript{10}

The clinical symptoms of meningococcal disease range from fever to meningitis or fulminant sepsis. All of our 10 patients had initial presentations of fever and decreased activity which may mimic viral illness and result in delayed diagnosis. The most common manifestation was meningitis (70\%) in our study, in which patients presented with vomiting and seizure attacks. In addition to symptoms of increasing intracranial pressure, a bulging fontanel is also a clue for CNS infection.\textsuperscript{10} Although \textit{N. meningitidis} can be isolated from the bloodstream in up to three quarters of patients, meningococcemia occurs in only 5 to 20\% of patients. Three patients (30\%) with meningococcemia had uneventful hospitalization, but sometimes it may progress rapidly to purpura fulminans, disseminated intravascular coagulation (DIC), hemodynamic collapse, adrenal hemorrhage or multi-organ failure.\textsuperscript{5} Few of our patients (30\%) had purpuric or petechial rash; among those, one had fulminate hospital course presenting with hypotension and respiratory failure. Finally, the patient was diagnosed with meningitis with meningococcemia. To our knowledge, cutaneous manifestation is often the first sign that leads to the clinical consideration of meningococcemia. However, purpura due to meningococcal infection during the neonatal period is rare, and only a few cases have been reported.\textsuperscript{10-12} Clinicians should still be aware of meningococcal infection in the presentation of purpura in the young infants.\textsuperscript{11,16}

The laboratory findings in severe bacterial infections including leukocytopenia, thrombocytopenia, and elevated C-reactive protein have also been observed. Examination of CSF reflected pyogenic meningitis which disclosed pleocytosis, raised protein levels and hypoglycorrachia. Coagulopathy was a distinguishing feature. Production of inflammatory cytokine and activation of both extrinsic and intrinsic pathways of coagulation in patients with meningococcal disease could result in capillary leakage and DIC.\textsuperscript{15} Prolonged PTT, low serum fibrinogen concentrations, low levels of protein C and antithrombin III are associated with significant morbidity or mortality in patients with invasive meningococcal disease.\textsuperscript{5,16} Serologic grouping is attributed to the outer polysaccharide capsule of \textit{N. meningitidis}, and at least 13 different serogroups have been identified. Groups A, B, C, Y, and W-135 are the major pathogens involved in human disease.\textsuperscript{3} For the patients treated at our institution, the most common serogroup identified was type B, followed by serogroup W-135. Researchers found a higher proportion of serogroup B disease occurred in children younger than 2 years, whereas serogroup C was relatively more common in older children, adolescents, and adults.\textsuperscript{1} In previously published reports in the literature, researchers described frequent extrameningeal complications in cases of serogroup W-135 infection,\textsuperscript{17,18} but there was no extrameningeal involvement in our study.

Penicillin remains the first choice of antimicrobial regimen in meningococcal disease with lower resistant rate. Cefotaxime and ceftriaxone are acceptable alternatives. Therapy in three patients with meningococcemia relied on the recommended duration of 5-7 days, and none relapsed or had subsequent complications. However, prolonged antibiotic treatments (range, 14 to 42 days) were required in six
patients with meningitis complicated with subdural empyema. Subdural effusion occurs in approximately 20% to 30% of infants with meningitis. Subdural effusion is commonly seen in patients with \textit{H. influenzae} type b meningitis and infrequently in patients with meningococcal meningitis. Approximately 1% of patients developed subdural empyema. Brain images including CT and MRI can distinguish between effusion and empyema, with the latter requiring prolonged antibiotics course and drainage. In our observations, meningitis in young infants was usually complicated with subdural empyema which was confirmed on brain CT. Only one patient received prolonged therapy for 6 weeks combined with craniotomy for drainage. Another one with subdural empyema was treated for 2 weeks with antibiotics, but subsequently developed long-term sequela. The optimal duration of antimicrobial therapy for subdural empyema is uncertain. Parenteral antimicrobial therapy is recommended to be continued for at least 3 weeks after neurosurgery, and then followed by 3 weeks of oral therapy. A longer parenteral course, typically 6 weeks, is necessary in patients without drainage procedures. In infants, conservative treatment may be sufficient, and surgery is requisite when patients have evidence of mass effects or medical failure.\(^{(19)}\)

Sequelae occur in approximately 10% of patients with meningococcal meningitis, and permanent neurologic deficits include hearing loss, seizure, hydrocephalus and development delays. The presumptive factors associated with our two patients with sequelae were insufficient antibiotic therapy for subdural empyema and infection by a penicillin resistant strain. The appearance of encephalomalacia on brain images was a poor prognostic factor for developing permanent neurologic deficits.\(^{(19,20)}\)

Recently, the strategy for control of meningococcal disease is routine immunization with quadrivalent polysaccharide vaccine which contains serogroups A, C, Y and W135. However, the limits of the vaccine include no effective immunity among children younger than 2 year-old, and no inclusion of serogroup B which is the predominant cause of endemic meningococcal disease among young children. Development of capsular polysaccharide-protein conjugate vaccines for the prevention of serogroup B infection as well as a vaccine effective among infants is important for the comprehensive control of meningococcal disease.\(^{(21-24)}\)

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腦膜炎雙球菌感染在小於六個月嬰孩的臨床表徵

黃宜蓉 陳慧玲 朱世明

背 景：腦膜炎雙球菌是兒童及青少年時期重要的細菌感染之一。隨著循環中母體抗體的消退，在嬰孩中的盛行率依然是很高，且常造成嚴重的侵犯性疾病。本研究的目的是試著分析腦膜炎雙球菌在小於6個月嬰孩的臨床表徵。

方 法：經由回溯性病例回顧，我們整理了長庚兒童醫院1994年到2004年間，所有發生在年齡小於6個月的腦膜炎雙球菌感染病例，分析其臨床表徵及其預後。

結 果：總共有10位男嬰孩，平均發病年齡為2.9 ± 1.79 月。所有的病例一開始的徵候都是以發燒和活力減退來表現。有6個病人發生抽筋的表現，只有3個病人有出血點或紫斑的皮膚表徵。檢驗結果顯示發炎指數升高(159.1 ± 108.8 mg/L)，脊髓液中的白血球增加(791.11 ± 660.83/μL)，蛋白質上升(190.43 ± 157.91g/dl)和低血糖(28 ± 20.89 mg/dl)。有7位病童診斷為腦膜炎，其中有2位血液也同樣培養出腦膜炎雙球菌。剩下3位為菌血症。盤尼西林是最常使用的抗生素藥物且對腦膜炎雙球菌的抗藥性低。在6位腦膜炎合併硬膜下膿瘡的病患，都需要延長藥物的使用天數。在積極治療之下，沒有死亡病例。長期追蹤，有兩位病患被診斷智力障礙，其中一位還合併癲癇。這兩位病患都是低體重児，初期意識狀態低下，白血球過低，有合併硬膜下膿瘡和腦實質軟化。一位病患其抗生素療法過短，一位是遭受對盤尼西林有抗藥性的腦膜炎雙球菌感染。

結 論：腦膜炎雙球菌感染的臨床表徵一開始的表現可能很難和病毒感染區分，但很快會進展至惡化的情況。所以臨床醫師須警覺腦膜炎雙球菌在嬰孩時期的感染。病患合併硬膜下膿瘡，都需要較長的抗生素使用天數。影像學證實有腦實質軟化在神經發育上的預後很差。

(長庚院誌2006;29:107-13)

關鍵字：腦膜炎雙球菌，硬膜下膿瘡，腦實質軟化。

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