Meningococcal Disease among Children Who Live in a Large Metropolitan Area, 1981–1996

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Neisseria meningitidis is an important cause of serious bacterial infections in children. We undertook a study to identify meningococcal infections of the blood, cerebrospinal fluid, or both of children in a defined geographic area to describe the burden of disease and the spectrum of illness. We reviewed the medical records of all children aged <18 years who had meningococcal infections at the 4 pediatric referral hospitals in Boston, Massachusetts, from 1981 through 1996. We identified 231 patients with meningococcal disease; of these 231 patients, 194 (84%) had overt disease and 37 (16%) had unsuspected disease. Clinical manifestations included meningitis in 150 patients, hypotension in 26, and purpura in 17. Sixteen patients (7%) died. Although meningococcal disease is devastating to a small number of children, we found that the burden of pediatric disease that it caused at the 4 pediatric referral centers in this geographic region was limited; that patients with overt meningococcal disease are most likely to have meningitis; and that individual practitioners are unlikely to encounter a patient with unsuspected meningococcal disease.

Neisseria meningitidis is a well-known cause of serious bacterial infections in children [1–4]. Since the introduction of the conjugate Hib vaccine, N. meningitidis has surpassed Haemophilus influenzae type b with regard to frequency of isolation in pediatric patients with meningitis [4], and with the routine use of pneumococcal conjugate vaccine, N. meningitidis will likely become the most common cause of bacterial meningitis in children. The annual incidence of meningococcal disease is ∼0.6–1.4 cases per 100,000 population [1, 4–8]. The majority of cases of invasive meningococcal disease occur in children aged <4 years, with a second peak in the age group of 15–24 years [1, 6–8]. Infection by this organism may cause overwhelming sepsis, typically characterized by shock and a hemorrhagic exanthem, or central nervous system involvement [8, 9]. Because of the morbidity and mortality associated with N. meningitidis, timely diagnosis is a constant concern for clinicians who evaluate febrile children.

Currently, meningococcal vaccine is not a routine component of the immunization schedule in children in the United States [10]. Phase 3 trials of meningococcal protein conjugate vaccines, however, are currently in progress [11]. We undertook this study to explore the burden of meningococcal infections in children within a defined geographic area by examining all cases of infection at the 4 pediatric referral centers in Boston, Massachusetts, over a 16-year period. Because the immunogenicity of meningococcal protein conju-
PATIENTS AND METHODS

**Data collection.** We reviewed the medical records of all children aged <18 years who had meningococcal infections diagnosed at 1 of the 4 medical school–affiliated pediatric referral hospitals in Boston. Patients were identified by a review of admission diagnoses, microbiology log books, and International Classification of Diseases, Edition 9, discharge coding by the medical records departments. We reviewed records from 1981 through 1996 at Children’s Hospital Boston/Boston City Hospital; from 1986 through 1996 at Massachusetts General Hospital; and from 1988 through 1996 at the Boston Floating Hospital for Children. Subsets of these children have been previously studied and reported elsewhere [13–17].

To estimate the completeness of our ascertainment, we obtained the number of all children aged <18 years with meningococcal disease reported to the Massachusetts Health Department during 1988–1996. For reasons of confidentiality, we were not permitted to access the names of these patients.

The following elements were abstracted from the medical records onto a standardized data collection sheet: demographic information, clinical manifestations at the time of presentation, laboratory results, therapy, complications, and outcome. All visits to a medical facility or hospital were recorded. Those encounters that began at the office of a primary physician or at a community medical center with subsequent referral to another institution for further evaluation were analyzed as if they were 1 continuous visit.

**Definitions.** Patients were considered to have a meningococcal infection if *N. meningitidis* was isolated from samples of the blood, CSF, or both. In addition, children with both a CSF pleocytosis and a positive result on a CSF rapid antigen test for meningococcal antigen were included, even if cultures of CSF remained sterile. Overt meningococcal disease (OMD) was defined by signs of meningeal inflammation and pleocytosis in the CSF, by evidence of sepsis (e.g., hypotension, poor perfusion, and hemorrhagic exanthem) that led to immediate admission to the hospital and the administration of iv antibiotics, or both. Patients were considered to have unsuspected meningococcal disease (UMD) if they had the following signs or symptoms: the patient (1) did not appear ill; (2) showed no laboratory evidence (e.g., thrombocytopenia or pleocytosis in the CSF) indicative of sepsis or meningitis; (3) was discharged to home from an outpatient visit with a diagnosis other than sepsis or meningitis (e.g., viral syndrome or otitis media); and (4) later had *N. meningitidis* isolated from blood cultures, CSF cultures, or both, that were obtained at the initial encounter. Children who had signs or symptoms that were suggestive of meningococcal disease but who had neither positive culture results nor positive rapid antigen test results were excluded from the analysis. Children with meningococcal disease who had been evaluated at an outpatient visit and discharged to their homes before hospitalization were not considered to have UMD if cultures were not obtained at the outpatient visits.

Specific clinical manifestations of OMD that were analyzed included hypotension, purpura, meningitis, pneumonia, septic arthritis, pericardial effusion, seizures, renal failure, and respiratory failure that required intubation and assisted ventilation. “Hypotension” was defined as blood pressure below the fifth percentile for age [18]. Purpura were accepted as being present on the basis of the descriptions of the treating clinicians. “Meningitis” was defined as the recovery of *N. meningitidis* from samples of the CSF, a positive result of a rapid antigen test for meningococcal antigen in association with a CSF pleocytosis of $\geq 10$ WBCs/mm$^3$ (if aged $>1$ month), or recovery of *N. meningitidis* from a blood culture alone but with a CSF pleocytosis of $\geq 10$ WBCs/mm$^3$ (if aged $>1$ month). Because neonates ($\leq 1$ month of age) may normally have CSF pleocytosis of $\leq 25$ WBC/mm$^3$, these patients were considered to have meningitis according to the aforementioned criteria if they had a CSF pleocytosis $>25$ WBC/mm$^3$ [19]. A diagnosis of pneumonia was made on the basis of chest radiographic findings. “Septic arthritis” was defined as a joint fluid WBC cell count of $\geq 50,000$ cells/mm$^3$ in association with a positive result on a blood or joint fluid culture. Pericardial effusion was diagnosed by means of echocardiography. Seizure activity was determined on the basis of a description in a progress note or a discharge diagnosis. Patients with renal failure had an elevation of the serum creatinine level such that dialysis was required.

Sequelae included the following permanent or long-lasting complications of the disease: scarring secondary to localized skin loss, partial or complete amputations, and permanent neurological impairments, including seizures. Patients were considered to have seizures as a complication of meningococcal disease if they were discharged on anticonvulsant medication. There were insufficient data regarding hearing loss to evaluate this as an outcome.

“Duration of hospitalization” was defined as the total number of days of therapy in the hospital. This did not include home iv antibiotic therapy and, therefore, did not include the total duration of iv antibiotic therapy. In addition, patients who died in the emergency department were not included in the calculation of duration of hospitalization. Patients with bacteremia who were treated solely as outpatients were included in this definition, however, and they were given a duration of hospitalization value of 0.
RESULTS

Patient population. We identified a total of 231 children from all 4 pediatric referral centers who satisfied inclusion criteria: 179 (78%) of the patients were from Children’s Hospital Boston, 19 (8%) were from Massachusetts General Hospital, 19 (8%) were from Boston Floating Hospital for Children, and 14 (6%) were from Boston City Hospital/Boston Medical Center. From 1988 through 1996, when data were available from all 4 institutions, 132 patients were identified, an average of 15 patients for each year (range, 7–28 patients). During the same period, the Department of Health received reports of 70 children with meningococcal infection in the greater Boston area. Figure 1 depicts the monthly distribution of patients, showing the lowest incidence in the summer months and the highest incidence in the late winter months. Serogrouping was available on 117 (51%) of the patients. Serogroup B was isolated in 66 (56%) of 117 patients; serogroup C in 45 (38%) of 117; serogroup W-135 in 3 (3%) of 117; and serogroup Y in 3 (3%) of 117. Most patients were boys, and most patients were aged <2 years. Clinical and laboratory descriptions are presented in table 1.

Spectrum of disease: OMD. OMD occurred in 194 (84%) of 231 patients. Twenty of these children were seen in a physician’s office or emergency department before admission but did not have blood samples obtained for culture at these visits (as documented in the hospital record). These previous visits occurred a median of 1 day (range, 0.5–3 days) before hospitalization. Fifty-five percent of patients with OMD were aged ≥2 years. The median age of patients with OMD was 28 months (range, 2 weeks to 18 years). Clinical manifestations of OMD included meningitis in 133 patients (68%), hypotension in 26 (13%), respiratory failure in 20 (10%), purpura in 15 (8%), seizures in 9 (5%), septic arthritis in 4 (2%), renal failure in 4 (2%), and pericardial effusion in 3 (2%). Some patients had more than 1 clinical manifestation.

A total of 6 patients had meningococcal disease, which was diagnosed according to positive results of CSF latex antigen tests: 4 were infected with serogroup C and 2 were infected with serogroup B. The CSF WBC count in these 6 patients had a range of 675 cells/mm³ to 16,000 cells/mm³, and all patients but 1 had petechiae or purpura; the remaining patient had gram-negative diplococci on Gram stain of the CSF. Two of these patients were treated with antibiotics before CSF specimens were obtained for culture. All other patients in this study had OMD diagnosed by a positive culture result for N. meningitidis.

With regard to sequelae among these 194 patients, 5 patients underwent amputation of at least 1 limb, 2 patients lost digits but not limbs, 4 patients had seizures and were discharged on anticonvulsant medication, 2 patients had permanent neurological deficits other than seizures, and 5 patients needed skin grafts. Four of the 5 patients who required skin grafts also had permanent neurological deficits. Fifteen patients (8%) with OMD died.

Spectrum of disease: UMD. UMD was diagnosed in 37 (16%) of 231 children. The proportion of patients with UMD was similar in each year (figure 2). Eighty-nine percent of patients with UMD were aged <2 years. Serogrouping was available on 22 (59%) of the 37 patients. Serogroup B was isolated in 14 (64%) of 22 patients; serogroup C in 7 (32%) of 22; and serogroup W-135 in 1 (5%) of 22. Clinical manifestations (which developed after the first visit) included meningitis in 17 patients (46%), hypotension in 1 (3%), purpura in 2 (5%), respiratory failure in 1 (3%), respiratory failure and seizures in 1 (3%), and pericardial effusion in 2 (5%). CSF specimens were obtained in 35 of 37 patients for whom UMD was diagnosed. CSF specimens were obtained at the initial outpatient visit in 11 of these patients. In another 24 patients, CSF specimens were subsequently obtained after the diagnosis of meningococcal disease was made. One patient who had pericardial effusion also had pneumonia. One (3%) of the patients with UMD died, but none of the patients with UMD required amputation, skin grafts, or developed permanent neurological deficits. Two patients with UMD were never admitted to the hospital because they did not appear ill at follow-up.

DISCUSSION

We identified 231 children with meningococcal infections at the 4 academic pediatric referral centers in metropolitan Boston during a 16-year period. During the last 9 years of the study period, when cases were obtained from all 4 centers, we identified 132 patients, an average of 15 patients per year. Pediatric patients at community hospitals who were not referred to an academic center were not identified. However, given the discrepancy between the number of patients that we identified and the number reported to the Massachusetts Department of Health during that time, it is likely that we identified the majority of pediatric patients with meningococcal infections in Boston during the study period.
Table 1. Clinical and laboratory descriptions of meningococcal infections in children.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>23 mo. (2 w to 18 y)</td>
<td>—</td>
</tr>
<tr>
<td>&lt;2 years of age, %</td>
<td>52</td>
<td>—</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>150 (65)</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>81 (35)</td>
<td>—</td>
</tr>
<tr>
<td>Temperature, mean °C ± SD</td>
<td>39.4 ± 1.1</td>
<td>220</td>
</tr>
<tr>
<td>WBC count, cells/mm³ (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14,400 (1600–60,500)</td>
<td>—</td>
</tr>
<tr>
<td>Median in children aged &lt;2 years</td>
<td>13,700 (1600–52,600)</td>
<td>113b</td>
</tr>
<tr>
<td>Patients with WBC counts of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5000 cells/mm³, % (WBC range)</td>
<td>12.6 (1600–4800)</td>
<td>—</td>
</tr>
<tr>
<td>&gt;25,000 cells/mm³, % (WBC range)</td>
<td>10.8 (25,000–60,500)</td>
<td>—</td>
</tr>
<tr>
<td>Median absolute neutrophil count, cells/mm³ (range)</td>
<td>10,315 (112–45,980)</td>
<td>208</td>
</tr>
<tr>
<td>Median absolute band count, cells/mm³ (range)</td>
<td>1682 (0–18,410)</td>
<td>196</td>
</tr>
<tr>
<td>Median duration of hospitalization, d (range)</td>
<td>8 (0–106)</td>
<td>166</td>
</tr>
</tbody>
</table>

*a Value from the visit at which the first positive culture or latex agglutination test was obtained.

*b For data regarding children <2 years of age, n = 117.

The annual reported incidence of meningococcal disease varies from ~0.6 to 1.4 cases per 100,000 population [1, 4–8]. One recent report from the New England area during 1993–1998 cited an overall incidence of 1.1 cases per 100,000 population [1], with a yearly incidence of 0.9–1.4 cases per 100,000. It has been noted that the incidence of meningococcal disease varies according to the season; studies published elsewhere have stated that the highest attack rates are in February and March and the lowest rates are in September [1, 6, 7, 20, 21]. The peak incidence in our study occurred in March; the nadir was in August. Case fatality rates have been reported elsewhere to be 8%–14% [1, 6, 20–22]. We found a slightly lower mortality rate of 7%. A higher rate of incidence of disease in children aged <2 years has been described elsewhere [1, 7], and this is supported by our findings. The majority of these infections (in which the serogroup was known) were caused by serogroup B, a finding consistent with earlier data collected by the Centers for Disease Control [20] but in contrast with more recent reports, which have documented an increased rate of incidence of serogroup Y [6, 7]. The paucity of patients with infections due to serogroup Y in our study population may be explained by the association of serogroup Y disease with older patients [6, 23]. Furthermore, the difference between our study and other recent reports may be due to changes in the epidemiology of meningococcal disease during the 16 years of our study period.

Meningitis has been reported to occur in 57%–93% of patients with meningococcal disease [1, 3, 6, 21]. In the present study, meningitis occurred in 69% of patients with OMD and developed in 46% of patients with UMD. Clinical manifestations of meningococcal disease that have been reported elsewhere include hypotension, purpuric lesions, pericardial effusion, arthritis, pneumonia, and otitis media [1, 3, 6, 17, 22, 24]. With the exception of pneumonia and otitis media, our study population had a similar spectrum of illness. Previous reports of pneumonia have been associated with serogroups Y and W-135 [23, 25–27], both of which were rarely isolated among our study patients. Therefore, the uncommon occurrence of meningococcal pneumonia may be explained by the relative infrequency of these serogroups in our population.

Among our patients, UMD accounted for at least 16% of infections. Although another report [28] described a higher rate of UMD in children at one of the participating centers in Boston, this difference may be explained by the changing nature and referral pattern of the medical centers during the 2 time periods.

Potential limitations of our study. We were not able to identify all cases of meningococcal disease at all 4 hospitals that occurred during the entire 16 years. During the earlier years of the study period, data were not available from 2 of the institutions because the microbiology log book was unavailable for those years. A study published elsewhere [1] reported 394 cases of meningococcal disease in New England among patients of all ages during a 5-year period, but it is difficult to extrapolate from these data how many children in that series resided in the greater Boston area. In addition, because of the retrospective
nature of our study, the completeness of clinical descriptions in the medical records could not be verified. Finally, although this was a large study of meningococcal disease, there were relatively few children with UMD. Therefore, the clinical features and outcomes of these children have to be interpreted with this limitation in mind.

CONCLUSION

In this 16-year review of meningococcal disease in children at the 4 academic pediatric referral centers in Boston, we found that, although the majority of patients had meningitis, the full spectrum of illness was also seen. Occurrence of disease was greatest in the winter and early spring. Manifestations of meningococcal disease were similar to those described elsewhere, with the exception of pneumonia, which we rarely observed among this pediatric and adolescent population. Furthermore, analysis of our data suggests a significant underreporting of disease to the Department of Health and may indicate a higher incidence of meningococcal disease nationwide than was previously thought.

We found that meningococcal disease, although it causes severe manifestations in a small number of children, produced a limited burden of illness in this geographic region. Even if all of the patients in the year with the highest incidence had presented to the largest hospital, only 28 (~0.06%) of the 50,000 visits to the emergency department and 28 (0.17%) of the 16,000 admissions to the hospital would have been the result of infection with *N. meningitidis*. Most of the children in this study with UMD were aged <2 years. In addition, given the 5 to 1 ratio of overt to unsuspected disease, analysis of our data suggests that an individual physician, unless practicing in a referral center or during the course of an epidemic of infection, is unlikely to encounter a patient with UMD.

Phase 3 trials for meningococcal protein conjugate vaccines are presently in progress [11]. Recommendations for meningococcal vaccines may soon be reconsidered, given the evolution of protein conjugate vaccines. Our current data provide baseline information about meningococcal disease in a large metropolitan area that may be used as a reference point in the prevaccine era.

References


