Serogroup Y Meningococcal Disease in Chicago, 1991-1997

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Context.—In 1994, surveillance by the Chicago Department of Public Health detected a growing trend in the proportion of invasive meningococcal infections caused by serogroup Y.

Objective.—To examine the emergence of serogroup Y meningococcal disease and compare its clinical characteristics with those of other meningococcal serogroups.

Design.—Population-based retrospective review of surveillance records; medical record review and cohort analysis of serogroup Y vs non–serogroup Y case patients.

Setting.—Chicago, Ill.

Participants.—City residents with Neisseria meningitidis isolated from a normally sterile site from January 1, 1991, through December 31, 1997; cohort analysis included those identified through March 31, 1996.

Main Outcome Measures.—Serogroup-specific incidence, demographics, and clinical outcomes.

Results.—We identified 214 case patients; 53 (25%) had serogroup Y. The attack rate of serogroup Y meningococcal disease increased from 0.04 cases per 100 000 in 1991 to a peak of 0.82 cases per 100 000 in 1995 and subsequently decreased to 0.26 cases per 100 000 and 0.34 cases per 100 000 in 1996 and 1997, respectively. Compared with patients infected by other serogroups, patients with serogroup Y were older (median age, 16 years vs 1 year; \( P = .001 \)) and more likely to have a chronic underlying illness (prevalence ratio, 2.3; 95% confidence interval, 1.2-4.4). Outcome did not differ significantly between the 2 groups. Multilocus enzyme electrophoresis typing of isolates from 19 case patients identified 5 different types. We found no clustering among the enzyme types by age, race/ethnicity, community area, or time.

Conclusions.—Serogroup Y emerged as the most frequent cause of meningococcal disease in Chicago in 1995 and accounted for a substantial proportion of cases in 1996 and 1997. Current data suggest that the magnitude of serogroup Y meningococcal disease is sufficient for vaccine developers to incorporate serogroup Y into new vaccines.

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MENINGOCOCCAL serogroup distribution has varied over time. In the United States, surveillance by the Centers for Disease Control and Prevention (CDC) demonstrated that during 1975 to 1980, serogroups B and C accounted for 56% and 19% of meningococcal isolates recovered from sterile sites (eg, blood or cerebrospinal fluid [CSF]). During 1989 to 1991, serogroups B and C occurred in approximately equal numbers, accounting for 91% of the total isolates. In contrast, serogroup Y accounted for only 2% of cases from 1989 through 1991 and was not specifically reported in the earlier surveys.

However, during certain periods, serogroup Y has accounted for a greater proportion of disease. The CDC found that serogroup Y accounted for 17% of the meningococcal strains isolated from CSF or blood investigated during November 1973 to March 1974 and January 1975 to April 1975. In addition, a population-based study of meningococcal disease in New York, NY, for the period 1973 to 1978 identified 14% of meningococcal isolates from CSF and blood as serogroup Y.

Despite its typically low prevalence, serogroup Y has been responsible for outbreaks of meningococcal disease. Smilack reported a military outbreak that included 12 cases of serogroup Y meningococcal disease (SYMD) among members of an army combat training unit. In this series, 5 patients had meningococemia, 5 had meningitis, and 2 presented with primary meningococcal pneumonia. Subsequently, a case series of SYMD was reported in a group of US Air Force recruits. In that series, the predominant manifestation of serogroup Y disease was respiratory; 68 (77%) of 88
patients had meningococcal pneumonia, documented by transtracheal aspirates in 94% of the cases. Only 4 (6%) of the 68 patients with pneumonia had positive blood cultures. In 1984, surveillance by the Chicago Department of Public Health detected a growing trend in the proportion of invasive meningococcal infections caused by serogroup Y. We conducted a population-based retrospective review of invasive meningococcal disease cases among residents of Chicago, Ill, to define the clinical spectrum of SYMD and to compare its characteristics with non-serogroup Y meningococcal disease (NSYMD). We sought to describe any patterns in the emergence of serogroup Y using traditional epidemiologic techniques and multilocus enzyme electrophoresis.

METHODS

To identify potential cases of meningococcal disease, we retrospectively reviewed all reports received by the Chicago Department of Public Health of persons with meningococcal disease in the city of Chicago that occurred from January 1, 1991, through December 31, 1997. Reporting of meningococcal disease to public health authorities is mandatory in Illinois; isolates that are not serogrouped by the reporting institution must be sent to the Illinois Department of Public Health laboratory for serogrouping. Referral for serogrouping has been required since mid 1992. To locate any cases that may not have been reported through the Chicago Department of Public Health surveillance system, we audited the logs of the Illinois Department of Public Health microbiology laboratory and reviewed the list of meningococcal disease cases maintained by the communicable diseases division of the Illinois Department of Public Health. To detect any unreported cases, we asked infection control practitioners at Chicago-area hospitals to review their records for patients with meningococcal disease.

Confirmed cases of meningococcal disease were defined by the isolation of Neisseria meningitidis from blood and/or CSF. All case patients were residents of the city of Chicago at the time of their illness; Chicago residents who were hospitalized outside the city limits during their illness were included in the series. Meningococcemia was defined as an abrupt-onset septic illness characterized by fever and chills, a positive blood culture for meningococcus, and 3 or more of the following symptoms or signs: nausea and vomiting; prostration; myalgia and arthralgia; diarrhea; tachypnea; a generalized maculopapular petechial, or purpuric skin rash; hypotension (systolic blood pressure <90 mm Hg); or coagulation abnormalities. Meningitis was defined as an illness distinguished by a CSF pleocytosis and fever, severe headache, meningeal irritation, or other meningeal signs, or altered mental status. Bacteremia without sepsis was defined by the growth of N meningitidis from blood cultures in patients with fever but without signs of meningococcemia or meningitis. The presence of pneumonia was ascertained by review of hospital discharge diagnoses.

For case patients who presented with meningococcal infection between January 1, 1991, and March 31, 1996, the medical record was reviewed by a physician using a standardized chart abstraction form to determine demographic characteristics, underlying illnesses, physical examination findings, clinical course, complications, and illness outcomes. We then performed a cohort analysis comparing patients with SYMD to patients with NSYMD. Case patients with meningococcal disease of unknown serogroup were excluded from the cohort analysis. Subsequently, we repeated the cohort analysis after classifying patients of unknown serogroup in the NSYMD group.

We calculated yearly attack rates by using population estimates based on extrapolations from 1990 census data for the city of Chicago. Census data from 1990 was used to calculate age-adjusted rates. A surrogate measure for low socioeconomic status was created by combining those case patients in the Medicaid and “no insurance or self-paid” categories. Information on median income also was collected for each patient based on his/her census tract of residence. The data were analyzed using Epi Info 6.0 software. Mantel-Haenszel $\chi^2$ tests were used for tests of statistical significance unless otherwise specified. Associations with $P<.05$ were considered statistically significant.

For all patients, we obtained isolate serogroup information from either the original hospital, the Illinois Department of Public Health microbiology laboratory, or both. Nineteen serogroup Y isolates available at the Illinois Department of Public Health microbiology laboratory were sent to the CDC for multilocus enzyme electrophoresis, using a panel of 24 enzymes. Three isolates dated from 1994, 13 from 1995, and 3 from 1996.

RESULTS

Between January 1, 1991, and December 31, 1997, there were 214 culture-confirmed cases of meningococcal disease. Serogroup classification was available for 172 (80%) of the 214 isolates. The distribution of meningococcal disease by serogroup was the following: Y, 25% (53/214); B, 20% (44/214); C, 29% (63/214); nontypeable, 4% (8/214); W-135, 1% (2/214); Z, 1% (2/214); and unknown, 20% (42/214).

The yearly attack rate for meningococcal disease in the city of Chicago ranged from 0.8 cases per 100 000 in 1991 to 1.9 cases per 100 000 in 1997 (Figure). Between 1991 and 1995, the incidence of SYMD increased 20-fold from 0.04 to 0.82 cases per 100 000, and the incidence of NSYMD decreased by 50%. The largest incremental increase occurred between 1994 and 1995, when the attack rate of
SYMD increased from 0.19 cases per 100,000 to 0.82 cases per 100,000. The attack rate of SYMD subsequently decreased to 0.26 cases per 100,000 and 0.34 cases per 100,000 in 1996 and 1997, respectively. At the same time, the attack rate of NSYMD rebounded in 1996 and continued to rise in 1997. This increase in NSYMD was attributable to an increase in the incidence of serogroup C from 0.1 cases per 100,000 in 1995 to 0.4 cases per 100,000 in 1996 and 1.0 case per 100,000 in 1997. Two case patients with serogroup C meningococcal disease were close contacts of a primary case; no other serogroup C case patients were known to be linked. At no time did the incidence of serogroup C meet the established criteria for linked. At no time did the incidence of serogroup C meningococcal disease was highest among children 2 years or younger (7.7 cases per 100,000). The rate declined with increasing age to a low in the 25- to 59-year group (0.3 cases per 100,000), and rose again for patients older than 60 years (0.6 cases per 100,000). The median age of patients with SYMD was higher than that of patients with NSYMD (Table 1). While still greater than that of NSYMD patients, the median age of SYMD patients dropped substantially in 1995 compared with the period 1991 to 1994 (11.5 vs 19 years; \( P = 0.01 \), Wilcoxon rank sum test).

Among these 132 case patients, 57% were black, 23% were non-Hispanic white, and 20% were Hispanic. Calculation of attack rates by year for individual race/ethnic groups revealed 2-fold to 3-fold higher attack rates among blacks compared with non-Hispanic whites and Hispanics. During 1991 to 1995, the attack rate ranged from 1.3 to 2.4 cases per 100,000 among blacks, from 0.6 to 0.8 cases per 100,000 among non-Hispanic whites, and from 0.5 to 0.8 cases per 100,000 among Hispanic persons. Age standardization of meningococcal disease rates did not remove the disparity between race/ethnic groups. Patients with SYMD had underlying illnesses twice as often as those with NSYMD (Table 1). The most common underlying conditions among SYMD case patients were diabetes mellitus (4/42 [9.5%]), chronic lung disease (3/42 [7.1%]), lupus (3/42 [7.1%]), premature birth (3/42 [7.1%]), and therapy with immunosuppressive agents (3/42 [7.1%]).

The frequency of presenting symptoms, signs, and laboratory findings differed for patients with SYMD compared with those with NSYMD (Table 3). Patients with SYMD were statistically more likely to present with sputum production and chest pain; however, these symptoms occurred infrequently overall, and were predominantly reported by patients older than 20 years. The frequency of cough did not differ between the 2 groups. Patients with SYMD were more likely to have meningococcemia (32/132 [24.0%]). Of the 61 patients with meningitis, 64% (39/61) had a positive blood culture. Fifteen percent (20/132) of the patients had a concurrent pneumonia. Meningitis was the most common diagnosis in case patients younger than 30 years. Bacteremia without sepsis was the most common diagnosis in persons older than 30 years. The number of case patients with a diagnosis of meningococcemia occurred in an age distribution consistent with the age distribution of all meningococcal disease cases. Pneumonia occurred more commonly in patients 40 years or older (10/20 [50%]).

The case fatality rate for all meningococcal disease was 11% (14/132). Nearly all persons who died had meningococcemia (13/14 [93%]); 5 (35%) of the 13 patients with meningococcemia also had meningitis. Meningitis alone caused the remaining death. Pathologic findings consistent with Waterhouse-Friderichsen syndrome (adrenocortical hemorrhage) were present in 70% (7/10) of the case patients with meningococcemia who were autopsied. The case fatality rate was 3-fold higher for case infants 35 years or older compared with those younger than 35 years (6/27 [22.2%] vs 8/105 [7.6%]; relative risk [RR]; 2.9; 95% confidence interval [CI], 1.1-7.7). Frequency of death due to meningococcal disease did not differ between race/ethnic groups or for high- vs low-socioeconomic status groups (as defined by income status). We found no significant difference in outcomes for SYMD vs NSYMD case patients (Table 2).

Thirty percent of case patients had an underlying illness that could have elevated their risk for contracting meningococcal disease. However, case patients with an underlying illness were not significantly more likely to die due to their meningococcal infection than previously healthy case patients. Patients with SYMD had underlying illnesses twice as often as those with NSYMD (Table 1).
less likely to present with petechiae or purpura or with evidence of meningococcal irritation than patients infected with non–serogroup Y serogroups; however, these latter 2 findings were of marginal statistical significance.

The manifestations of clinical illness associated with SYMD differed from the other serogroups. Whereas the occurrence of meningitis was similar between patients infected with serogroup Y and non–serogroup Y strains, patients with SYMD were more likely to be diagnosed as having bacteremia without sepsis (17/42 [40%] vs 15/63 [24%]); RR, 1.7; 95% CI, 1.0-3.0) and less likely to be diagnosed as having meningococcemia (6/42 [14%] vs 17/63 [27%]; RR, 0.5; 95% CI, 0.2-1.2). These differences did not achieve statistical significance, however. We did not find any association between SYMD and the presence of an infiltrate on admission chest radiograph or a discharge diagnosis of pneumonia.

The comparison of SYMD and NSYM was complicated because of the inclusion of patients with unknown serogroups in the latter group. The results of this secondary analysis did not differ substantially from the results previously described.

Multilocus enzyme electrophoresis of 19 serogroup Y isolates collected over a 3-year period identified 5 different enzyme type patterns. The most prevalent enzyme type among the isolates tested, type 508, accounted for 7 (37%) of the isolates. Five isolates were enzyme type 516, previously detected in serogroup Y isolates from the 1970s (M. Reeves, PhD, CDC, written communication, August 1996). Enzyme types 508 and 516 differed by 2 enzymes.

One 1970s and then nearly disappeared subsequently, the emergence and subsequent decline to 18% by 1997. Patients with SYMD were more likely to be older and black than NSYM patients. Patients with SYMD tended to have underlying medical conditions and present with respiratory symptoms more often than patients with NSYM. Despite differences in demographics and clinical presentations, there was no statistically significant difference in outcomes between SYMD and NSYM patients.

The emergence of SYMD in Chicago is part of a national trend. A recent Morbidity and Mortality Weekly Report presented data from the CDC active surveillance areas for meningococcal disease (encompassing 12 million people); during 1989 to 1995, the proportion of serogroup Y meningococcal isolates from sterile sites increased from 0% to 32.5%.12 The timing of the emergence of SYMD was similar to that in Chicago, with most of the increase occurring between 1994 and 1995. Since 1995, in contrast with Chicago, the proportion of cases due to serogroup Y in the CDC surveillance areas has not declined (N. Rosenstein, MD, CDC, unpublished data, March 1998). It is unclear why serogroup Y became the most common cause of meningococcal disease in Chicago in 1995 and then declined, although not yet to previous levels. In Chicago, no clustering occurred among cases, and overall attack rates for meningococcal disease remained below what would be considered outbreak levels for serogroup C disease (10 cases per 100 000 population for a 3-month period).13 Furthermore, in contrast to what has been described with other meningococcal disease outbreaks, we observed a shift toward a lower median age of SYMD patients in 1995. Consequently, the emergence and subsequent decline of serogroup Y represents a shift in endemic serogroups rather than an outbreak of disease. One possible explanation for the emergence would be that immunity to serogroup Y has waned in the community, resulting in more disease. Subsequently, with increased exposure to serogroup Y, immunity may have increased enough to cause a decline. The observation that SYMD peaked in the mid 1970s and then nearly disappeared supports this hypothesis.

Alternatively, the rise in SYMD could partially result from the emergence of a new clone or clonal group locally. Unfortunately, we were unable to test this hypothesis because the distribution and prevalence of serogroup Y multilocus enzyme electrophoresis types for the last decade is unknown. We found no patterns by time, age, race/ethnicity, or neighborhood among the 5 enzyme types identified in our sample of 19 isolates. However, 9 of the 22 serogroup Y isolates from 1995 were not available for typing, so we could not rule out the possibility of some clustering by enzyme type.

Finally, serogroup Y strains could have evolved to become more invasive in recent years. Our data do not support this hypothesis, however. Patients with SYMD tended to have meningococcemia less often and bacteremia without sepsis more often than patients with NSYM. Some investigators have postulated that serogroup Y has a more benign course than other meningococcal serogroups.6 Our observation that SYMD was more common among patients with chronic underlying diseases but did not induce more frequent serious outcomes supports the suggestion that this serogroup may be less virulent than others.

Other studies have identified a predilection of serogroup Y meningococcus for causing respiratory illness, including a large outbreak of predominantly respiratory SYMD in a group of Air Force recruits.6 Although older patients with SYMD in this study presented more often with symptoms of pneumonia, including purulent sputum and chest pain, they did not present more frequently with a cough or an infiltrate on admission chest radiograph. The symptoms described could have been evidence of bronchitis and not pneumonia; alternatively, pneumonia may have been underdiagnosed once a patient was found to have meningitis or meningococcemia.

Table 3.—Presenting Symptoms, Signs, and Laboratory Findings of Patients With Known Serogroups

<table>
<thead>
<tr>
<th>Clinical or Laboratory Finding</th>
<th>Serogroup Y Meningococcal Disease, No. (%)</th>
<th>Non–Serogroup Y Meningococcal Disease, No. (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>8 (19%)</td>
<td>1 (1.6)</td>
<td>12.0 (1.9-92.4)</td>
</tr>
<tr>
<td>Sputum</td>
<td>6 (14.3)</td>
<td>1 (1.6)</td>
<td>9.0 (1.1-72.1)</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 (7.1)</td>
<td>2 (3.2)</td>
<td>2.2 (0.4-12.9)</td>
</tr>
<tr>
<td>Infiltrate on admission chest x-ray</td>
<td>7 (22.6)</td>
<td>9 (19.1)</td>
<td>1.2 (0.5-2.6)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>4 (9.5)</td>
<td>5 (7.9)</td>
<td>1.2 (0.2-5.6)</td>
</tr>
<tr>
<td>Cough</td>
<td>15 (35.7)</td>
<td>24 (38.1)</td>
<td>0.9 (0.5-1.6)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>12 (28.6)</td>
<td>23 (36.5)</td>
<td>0.6 (0.4-1.4)</td>
</tr>
<tr>
<td>Petechia or purpura</td>
<td>9 (21.4)</td>
<td>25 (39.7)</td>
<td>0.5 (0.3-1.0)</td>
</tr>
<tr>
<td>Focal neurologic deficit</td>
<td>1 (2.4)</td>
<td>3 (4.8)</td>
<td>0.5 (0.0-4.6)</td>
</tr>
<tr>
<td>Meningeal irritation</td>
<td>7 (16.7)</td>
<td>22 (34.9)</td>
<td>0.5 (0.2-2.0)</td>
</tr>
<tr>
<td>Cerebrospinal fluid white cell count $&gt;5$/hpf</td>
<td>21 (81)$†$</td>
<td>37 (68)$¶$</td>
<td>1.2 (0.9-1.5)</td>
</tr>
<tr>
<td>Cerebrospinal fluid white cell count $&gt;1000$/hpf</td>
<td>9 (35)$†$</td>
<td>23 (42)$¶$</td>
<td>0.8 (0.4-1.5)</td>
</tr>
<tr>
<td>Gram-negative diplococci on cerebrospinal fluid Gram stain</td>
<td>12 (46)$†$</td>
<td>20 (37)$¶$</td>
<td>1.2 (0.7-2.0)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; hpf, high-power field. Mantel-Haenszel $\chi^2$ tests were used to test for significant statistical differences between the 2 groups.
†The total number of patients in the group is 26.
‡The total number of patients in the group is 54.

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Finally, we may have underdetected cases of pneumonia because radiological reports were not always present in the medical records; we depended on discharge diagnoses to determine whether a patient had pneumonia. Our study would not have identified patients with pneumonia unless bacteremia were present because reporting of noninvasive meningococcal illness is not mandatory in Illinois. Given the suggestion of an association between serogroup Y meningococcus and respiratory disease, detection of N meningitidis serogroup Y from sputum or blood of patients with pneumonia may be clinically relevant.

When the incidence of SYMD increased 4-fold from 1994 through 1995, there was a disproportionate increase among blacks compared with the other racial/ethnic groups. It is unknown why this group had higher rates of meningococcal infection, especially serogroup Y. Meningococcal disease has been linked to factors associated with low socioeconomic status (eg, crowded living conditions or parental smoking). We did not find an association between SYMD and income level, however. Our study design did not allow assessment of other factors that could explain the higher incidence of SYMD among blacks in the cohort.

Because serogroup Y has been an important cause of invasive meningococcal disease in Chicago and elsewhere in recent years, those developing new meningococcal vaccines for use in the United States should consider additional evaluation of serogroup Y. A quadrivalent vaccine containing serogroup A, C, Y, and W135 polysaccharides (Comnaught Laboratories Inc, Swiftwater, Pa) is currently available in the United States. The vaccine is recommended for outbreaks caused by serogroup C and as routine immunization for military recruits and certain persons at high risk (eg, those with asplenia or terminal complement deficiencies).

Currently, US policy does not recommend routine immunization for control of endemic disease of any serogroup due to poor vaccine immunogenicity in infants and young children. Conjugated vaccines similar in structure to those now in use for Haemophilus influenzae type b may be more promising for preventing disease in infants and are being evaluated for meningococcal serogroups C and A. In view of current national serogroup incidence patterns, inclusion of a serogroup Y component should be considered if a multivalent conjugate vaccine were to be developed for use in the United States.

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