The Role of Particular Strains of *Neisseria meningitidis* in Meningococcal Arthritis, Pericarditis, and Pneumonia

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The clinical presentations of meningococcal diseases other than meningitis or meningococcemia may lead to erroneous diagnosis. Although several reports have described unusual meningococcal diseases, the *Neisseria meningitidis* strains involved in these forms have been poorly characterized. In this study, meningococcal arthritis and pericarditis were confirmed by isolation of *N. meningitidis* and/or detection of meningococcal DNA in synovial or pericardial fluid, respectively, and meningococcal pneumonia was detected by isolation of *N. meningitidis* from blood. From 1999 through 2002, meningococcal disease was bacteriologically confirmed in 26 cases of arthritis, 6 cases of pericarditis, and 33 cases of pneumonia by the National Reference Center for the Meningococci in Paris. We found a statistically significant association between strains of serogroup W135, mostly of the clonal complex ET-37, and arthritis. Pneumonia was most frequently diagnosed in patients aged >70 years, and 54.5% of the strains belonged to serogroup W135, although these strains had heterogeneous phenotypes. Bacteremia is a key step in the pathophysiology of meningococcal disease and precedes any form of invasive infection.
METHODS

Bacteriologic identification and typing. We considered only septic meningococcal infections (i.e., those in which bacteria were isolated from individuals with invasive infections, with an increasing annual incidence of ~10% (table 1). Serogroup B was the most frequent, although the relative proportion of serogroup B isolates decreased from 69% in 1999 to 49% in 2002. The overall increase in the incidence of meningococcal disease was mainly associated with an increase in the incidence of serogroup C disease since 2001 [8]. After the first case of serogroup W135 meningococcal disease was detected, in 1994, the incidence of such disease continuously increased, reaching 9.3% in 2002. Serogroup Y was stably present. In 2001, the incidence of serogroup C disease since 2001 [8]. After the first case of serogroup W135 meningococcal disease was detected, in 1994, the incidence of such disease continuously increased, reaching 9.3% in 2002. Serogroup Y was stably present. In 2001, the incidence of serogroup C disease since 2001 [8]. After the first case of serogroup W135 meningococcal disease was detected, in 1994, the incidence of such disease continuously increased, reaching 9.3% in 2002.

Clinical data. Each clinical isolate was accompanied by a questionnaire containing data on the patient’s identity, the sample collected, the date of the sample collection, and the clinical diagnosis at admission to the hospital, as well as epidemiologic data on the patient’s geographic origin and any relationship to another case of meningococcal disease.

Statistical analysis. Statistical analysis was done for bacteriologically confirmed cases by the chi-square test with the Mantel-Haenszel correction. P < .05 was considered to be statistically significant.

RESULTS

General characteristics of meningococcal strains isolated in France. During the period 1999–2002, 2091 strains of N. meningitidis were isolated from individuals with invasive infections, with an increasing annual incidence of ~10% (table 1). Serogroup B was the most frequent, although the relative proportion of serogroup B isolates decreased from 69% in 1999 to 49% in 2002. The overall increase in the incidence of meningococcal disease was mainly associated with an increase in the incidence of serogroup C disease since 2001 [8]. After the first case of serogroup W135 meningococcal disease was detected, in 1994, the incidence of such disease continuously increased, reaching 9.3% in 2002. Serogroup Y was stably present. In 2001, the incidence of serogroup C disease since 2001 [8]. After the first case of serogroup W135 meningococcal disease was detected, in 1994, the incidence of such disease continuously increased, reaching 9.3% in 2002.

Table 1. Neisseria meningitidis strains of various serogroups isolated from individuals with invasive infections in France, 1999–2002.

<table>
<thead>
<tr>
<th>Year</th>
<th>B</th>
<th>C</th>
<th>A</th>
<th>Y</th>
<th>W135</th>
<th>Nonserogroupable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>287 (69.2)</td>
<td>92 (22.2)</td>
<td>2 (0.5)</td>
<td>15 (3.6)</td>
<td>16 (3.9)</td>
<td>3 (0.7)</td>
<td>415</td>
</tr>
<tr>
<td>2000</td>
<td>336 (65.9)</td>
<td>104 (20.4)</td>
<td>2 (0.4)</td>
<td>10 (2.0)</td>
<td>55 (10.8)</td>
<td>3 (0.6)</td>
<td>510</td>
</tr>
<tr>
<td>2001</td>
<td>288 (52.3)</td>
<td>197 (35.8)</td>
<td>4 (0.7)</td>
<td>16 (2.9)</td>
<td>39 (7.1)</td>
<td>7 (1.3)</td>
<td>551</td>
</tr>
<tr>
<td>2002</td>
<td>301 (48.9)</td>
<td>235 (38.2)</td>
<td>1 (0.2)</td>
<td>16 (2.6)</td>
<td>57 (9.3)</td>
<td>5 (0.8)</td>
<td>615</td>
</tr>
</tbody>
</table>

The majority of the cases were reported as monoarthritis (21 of 26 cases): of a knee in 12 cases, a hip in 5 cases, an ankle in 2 cases, and a shoulder in 2 cases. Arthritis was associated with bacteremia in 3 cases and with meningitis in 1 case. The mean age of the patients was 21 years (range, 3 months to 73 years), and the ratio of males to females was 0.69. The 8 strains of serogroup B that were involved in arthritis had heterogeneous phenotypes (B:4:P1-15; B:4:P1-4; B:4:nonsubtypeable [NST]; B:14:NST; B:15:P1-12,13; B:nonsubtypeable [NT]:P1-1,7; B:NT:P1-6; and B:NT:NST). Among the 7 strains of serogroup C, 4 had the phenotype C:2a:P1-5 and belonged to the major clonal complex ET-37 [9]. One strain was C:2a:NST, and 2 were C:2b:P1-2,5. Four of 6 serogroup W135 strains had a similar phenotype (2a:P1-2,5) and belonged to the clonal complex ET-37. Three of these W135 strains corresponded to cases in chil-
children (aged 3 months, 9 months, and 3 years) who were close contacts of pilgrims returning from the 2000 Hajj [10]. No statistically significant association was observed between arthritis and strains of serogroups B or C ($P > 0.1$ and $P > 0.8$, respectively), but this association was statistically significant for strains of serogroup W135 ($P < 0.002$) (table 2).

Six cases of primary meningococcal pericarditis were recorded. One C:2a:NST strain was isolated from pericardial fluid from a 15-year-old boy, and 5 other cases were confirmed by the detection of meningococcal DNA in pericardial fluids, including 2 cases resulting from infection with a serogroup C strain (2 infants, aged 1 and 8 months), 2 with serogroup W135 (2 children aged 18 months), and 1 with serogroup Y (a 52-year-old man). In 7 other cases, signs of pericarditis or myocarditis were present, but meningococcal meningitis or meningococcemia was confirmed bacteriologically; therefore, pericarditis or myocarditis was considered to be a secondary complication, and these cases were not included in our study.

**Meningococcal pneumonia.** Meningococcal pneumonia was identified on the basis of classical symptoms and signs (fever, dyspnea, cough, and radiologic findings) associated with the isolation of *N. meningitidis* from blood. Cases of broncho-pulmonary pneumonia (mostly chronic obstructive pulmonary disease) in which the results of culture of transtracheal or bronchoalveolar aspirates were positive but blood cultures were not done (on average, 100 strains per year) were rejected, because *N. meningitidis* can be found in the respiratory tracts of asymptomatic carriers [11]. Moreover, associated commensal flora were also isolated from respiratory samples, at bacterial loads often equivalent to that of the meningococci. Thirty-three cases of acute pneumonia, including 3 fatal cases, were recorded. An association between pneumonia and meningitis was noted in only 1 case.

The majority of the patients with meningococcal pneumonia (20 of 33 patients) were aged >70 years, and 11 were aged 40–70 years. No cases were recorded in patients aged <15 years. One case occurred in a 15-year-old boy, and another occurred in a 23-year-old man. The ratio of males to females was 1.35. An underlying disease was mentioned in 4 cases: cancer of the lung in a 75-year-old patient and 3 cases of cirrhosis in patients aged 52, 49, and 55 years. Eighteen strains (54.5%) from patients with meningococcal pneumonia were of serogroup W135, with heterogeneous phenotypes, including 5 strains of type W135:2a:P1-2,5 that belonged to the clonal complex ET-37. Three of these strains were isolated from March through May 2000, but only 1 case (of fatal pneumonia, in a 68-year-old woman returning from Saudi Arabia) was directly related to the outbreak among Hajj pilgrims in 2000 [10]. The other 13 serogroup W135 strains had the following phenotypes: NT:P1-6 (4 strains); NTP1-1-2 (2 strains); NT:P1-5 (2 strains); 2a:NST; NT:P1-1,7; NT:P1-2; NT:P1-16; and NT:NST. Nine strains were of serogroup C, including 4 strains of C:2a:P1-5 and 1 strain each of C:2a:P1-14, C:2a:NST, C:2b:P1-5, C:NT:P1-1, and C:NT:P1-2,5. Three strains were of serogroup Y, including 1 each of Y:15:P1-5, Y:NT:P1-5, and Y:NT:NST. Two strains were of serogroup B, including 1 each of B:1:NST and B:NT:NST. One strain was of type X:4:P1-16.

### Table 2. Serogroup distribution of *Neisseria meningitidis* isolates from individuals with bacteriologically confirmed cases of meningococcal septic arthritis.

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Synovial fluid</th>
<th>Other</th>
<th>Total</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>8</td>
<td>1254</td>
<td>1262</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>638</td>
<td>645</td>
<td>&gt;.8</td>
</tr>
<tr>
<td>W135</td>
<td>6</td>
<td>176</td>
<td>182</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>2068</td>
<td>2089</td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

Meningococcal diseases are medical emergencies, but early initiation of appropriate antibiotic therapy, especially with β-lactams, is effective [12]. However, any delay may lead to a fatal evolution when a septic syndrome, especially purpura fulminans, occurs [1–3]. Therefore, an accurate and rapid etiologic diagnosis is mandatory.

According to published records, meningococcal arthritis and pericarditis may be divided into 2 categories. The first is primary septic arthritis or pericarditis occurring at the onset of the meningococcal disease; in such cases, the bacteria are found in the synovial or pericardial fluid [4, 13–16]. The second is reactive arthritis or pericarditis that is a late complication of meningococcal disease, occurring 6–16 days after the initiation of treatment of a meningococcal disease. Such cases may be attributed to an immunopathologic process, and no bacteria are detectable in the synovial or pericardial fluids [4, 17]. In our study, 22 of 26 cases may correspond to primary septic arthritis, because *N. meningitidis* was detected in synovial fluid. Septic arthritis was associated with bacteremia in 3 cases and with meningitis in 1 case. Among 6 patients with pericarditis, a culture positive for *N. meningitidis* could be obtained in 1 case only, whereas the other cases were detected by PCR. Only 2 of these patients had signs of meningitis.

The association between strains of serogroup W135 and arthritis that we observed in the present study may be the result of the overrepresentation of strains belonging to the clonal complex ET-37 among W135 strains during the study period (data not shown). Strains of serogroup W135 (ET-37) seem to be increasingly isolated worldwide since 2000 [18]. The fact that several serogroup C strains involved in arthritis belonged to the clonal complex ET-37 is a further argument supporting...
a probable association between arthritis and strains of this clonal complex, rather than an association with a particular serogroup.

Moreover, our study focused only on culture- or PCR-confirmed septic meningococcal arthritis and pericarditis, and our results show that molecular diagnosis and typing methods may be of great help in the diagnosis of these septic forms, for which culture may fail. The clinical presentation of primary meningococcal pneumonia is indistinguishable from that of pneumococcal pneumonia, and, in the majority of cases, blood is cultured in an attempt to identify a suspected pneumococcal strain [19, 20]. Instead, N. meningitidis is isolated, and therefore a diagnosis of meningococcal disease is made [21, 22].

In our study, meningococcal pneumonia was mostly found in patients >70 years of age (median age, 70 years; mean age, 60.9 years), and the prominent serogroup was W135. In a review of 58 cases of meningococcal pneumonia recorded between 1974 and 1998 in the United States, Winstead et al. [22] reported that the median age of the patients was 57.5 years (mean age, 48.1 years) and that serogroup Y was predominant. Although both studies indicate that aging is a predisposing factor for meningococcal pneumonia, the underlying conditions reported in 29 of the 58 cases recorded by Winstead et al. [22] and in only 4 of 33 cases in our study could explain the difference in the mean ages of the patients in these reports. The discrepancies between the studies may also reflect distinct epidemiologic conditions. In particular, serogroup Y represented only 16.7% of the strains in our study, whereas serogroup W135 was prominent (present in 54.5% of cases). Although pulmonary infection may be an important source of airborne transmission to contacts, no secondary cases were recorded.

Culture of blood was essential for assessing the cause of the pneumonia. Using isolation of N. meningitidis from respiratory samples (sputum, bronchial or transtracheal, or even bronchoalveolar aspirates) to make a diagnosis might be misleading, especially when associated commensal flora are isolated, because N. meningitidis is frequently found in the respiratory tracts of asymptomatic carriers [11].

References


