Childhood bacterial meningitis in Bulgaria: a population-based retrospective study in six regions during 1992–96

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Objectives: We conducted a study to provide information on the importance of bacterial pathogens causing childhood meningitis in Bulgaria.

Methods: A 5-year population-based retrospective survey for bacterial meningitis in children <5 years of age was performed at all hospitals in the six largest regions of Bulgaria.

Results: There were 297 cases of meningitis reported, of which 211 (71.0%) were classified as bacterial in origin. The most common causes were Neisseria meningitidis (49 cases) and Haemophilus influenzae type b (Hib) (44 cases), accounting for 36% and 32% of etiologically confirmed cases. Thirty-one cases (70.5%) of Hib meningitis occurred in children <2 years of age, and 26 (59.1%) occurred in children 6–23 months of age. Average annual incidence rates of Hib meningitis based on the population of children <5 years of age for each region ranged from 1.3 to 9.8 per 100 000 (mean 5.9/100 000).

Conclusion: The estimated incidence rates from this study were similar to those reported from southern European and Mediterranean countries. Further studies are planned to provide information on appropriate strategies for preventing childhood meningitis in Bulgaria.


INTRODUCTION

Bacterial meningitis is one of the most serious pediatric infectious diseases, despite the introduction of new antibiotic agents and the availability of intensive care treatment. Many clinical and etiologic studies performed over the past 30 years have demonstrated that Haemophilus influenzae type b (Hib), Neisseria meningitidis and Streptococcus pneumoniae are the leading causative organisms of bacterial meningitis worldwide. Recently, special attention has been paid to Hib, because Hib meningitis and other invasive Hib diseases have been virtually eliminated through the widespread use of polysaccharide–protein conjugate vaccines in most industrialized countries.

In Bulgaria, information on the importance of Hib and other bacterial pathogens causing meningitis in childhood has been scarce and only derived from case series and outbreak investigations. This report presents the findings of a 5-year retrospective survey of pediatric meningitis in the six largest regions in Bulgaria.

METHODS

We conducted a retrospective review of all cases of clinical meningitis diagnosed among children 0–59 months of age between 1 January 1992 and 31 December 1996 at pediatric and infectious disease departments of all hospitals in the six largest regions in Bulgaria. The six regions are: Pleven Region, Plovdiv Region, Sofia City (the capital of the country), Sofia Region, Stara Zagora Region, and Varna Region. Altogether, Bulgaria is divided into 28 regions, and the 1996 national census showed a total population of 8.3 million. For the six regions included in the study, there was a total 1996 population of 3.3 million persons, of whom 149 431 were children younger than 5 years of age.

For each hospital, medical charts were examined for any children 0–59 months of age with an admission diagnosis or a discharge diagnosis of meningitis. A
standard protocol was used to collect data concerning demographic characteristics and clinical history for each patient. We also examined all laboratory reports, and recorded the identity of the etiologic organism, if known, for all cases of bacterial meningitis.

Patients were classified according to case definitions provided in a protocol developed by the World Health Organization (WHO). A suspected case of meningitis was defined as a child <5 years of age presenting with clinical symptoms of meningitis, e.g. fever, headache, stiff neck, bulging fontanelle, or mental status change. A probable case of bacterial meningitis was defined as a suspected case with turbid cerebrospinal fluid (CSF), or CSF with elevated protein (>100 mg/dL), decreased glucose (<40 mg/dL), or leukocytosis (>100 white blood cells/mm³) with >80% neutrophils. A confirmed case of bacterial meningitis was defined as a probable case with identification of an organism in the CSF by culture or latex agglutination test.

RESULTS

During the 5-year period (1 January 1992 to 31 December 1996), there were 297 cases of clinical meningitis among children 0–59 months of age at hospitals in the six regions. Based on laboratory investigations of CSF, 211 (71%) cases were classified as probable bacterial meningitis, and 86 (29%) were classified as probable viral meningitis. Based on culture reports, an etiologic agent was identified in 131 (64.9%) of the 211 patients with bacterial meningitis, while no specific organism was detected in the remaining 35.1% (Table 1).

N. meningitidis and Hib were the most common etiologic agents, accounting for 49 cases (23.2%) and 44 cases (20.9%), respectively. Twenty-one cases (10.0%) were due to S. pneumoniae. When only etiologically confirmed cases of bacterial meningitis are included, the proportions rise to 35.8% N. meningitidis, 32.1% Hib, and 15.3% S. pneumoniae (Figure 1).

Table 1. Meningitis in children 0–59 months of age in six regions of Bulgaria, 1992–96

<table>
<thead>
<tr>
<th>Organism</th>
<th>Sofia City</th>
<th>Sofia Region</th>
<th>Plovdiv</th>
<th>Varna</th>
<th>Pleven</th>
<th>Stara Zagora</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>N. meningitidis</td>
<td>12</td>
<td>24.0</td>
<td>7</td>
<td>28.0</td>
<td>10</td>
<td>20.8</td>
<td>7</td>
</tr>
<tr>
<td>H. influenzae type b</td>
<td>24</td>
<td>48.0</td>
<td>2</td>
<td>8.0</td>
<td>9</td>
<td>18.8</td>
<td>2</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>1</td>
<td>2.0</td>
<td>4</td>
<td>16.0</td>
<td>7</td>
<td>14.6</td>
<td>3</td>
</tr>
<tr>
<td>Other*</td>
<td>4</td>
<td>8.0</td>
<td>1</td>
<td>4.0</td>
<td>6</td>
<td>12.5</td>
<td>5</td>
</tr>
<tr>
<td>None Identified</td>
<td>9</td>
<td>18.0</td>
<td>11</td>
<td>44.0</td>
<td>16</td>
<td>33.3</td>
<td>17</td>
</tr>
<tr>
<td>Bacterial</td>
<td>50</td>
<td>100.0</td>
<td>25</td>
<td>100.0</td>
<td>48</td>
<td>100.0</td>
<td>34</td>
</tr>
<tr>
<td>Viral</td>
<td>12</td>
<td>17.0</td>
<td>17</td>
<td>25.0</td>
<td>7</td>
<td>20.0</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>42.0</td>
<td>65</td>
<td>42.0</td>
<td>65</td>
<td>41.0</td>
<td>41</td>
</tr>
</tbody>
</table>

* Including Streptococcus group A, B; Staphylococcus; Candida albicans; Mycobacterium tuberculosis; Pseudomonas aeruginosa, Proteus mirabilis, etc.

Figure 1. Proportions due to different causative organisms of etiologically confirmed cases of bacterial meningitis in children 0–59 months of age in six regions of Bulgaria, 1992–96.

Of the six regions, Sofia City was the only one where Hib ranked first as a causative agent, with 24 (48.0%) cases of meningitis due to Hib versus 12 (24.0%) due to N. meningitidis (Table 1).

Thirty-one (70.5%) of the patients with Hib meningitis were children younger than 2 years of age, and most of them (26 cases, 59.1%) were 6–23 months of age (Table 2). The age distribution of cases due to N. meningitidis was similar. In contrast, the age distribution was more uniform for patients with S. pneumoniae meningitis.

Over the 5-year period 1992–96, the average annual incidence rates for children 0–59 months of age were 6.6/100 000 for N. meningitidis, 5.9/100 000 for Hib, and 2.8/100 000 for S. pneumoniae. By region, the average annual Hib incidence among children 0–59 months of age ranged from 1.3/100 000 in Pleven to 9.8/100 000 in Sofia City. The average annual incidence rate of Hib meningitis was higher during the last 2 years of the study.
Table 2. Bacterial meningitis by etiologic agent and age group in six regions of Bulgaria, 1992-96

<table>
<thead>
<tr>
<th>Cases by agent</th>
<th>Age group (months)</th>
<th>0-5</th>
<th>6-23</th>
<th>24-59</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>N. meningitidis</td>
<td></td>
<td>4</td>
<td>8.16</td>
<td>29</td>
<td>32.65</td>
</tr>
<tr>
<td>H. influenzae type b</td>
<td></td>
<td>5</td>
<td>11.36</td>
<td>26</td>
<td>59.18</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td></td>
<td>8</td>
<td>38.10</td>
<td>8</td>
<td>38.10</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>14</td>
<td>60.87</td>
<td>5</td>
<td>21.74</td>
</tr>
<tr>
<td>Unidentified</td>
<td></td>
<td>33</td>
<td>44.59</td>
<td>20</td>
<td>27.03</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>64</td>
<td>30.33</td>
<td>88</td>
<td>41.72</td>
</tr>
</tbody>
</table>

Table 3. Proportion and average annual incidence rate of Hib meningitis per 100 000 children 0–59 months of age in five regions of Bulgaria compared with Sofia City Region during 1992–94 and 1995–96

<table>
<thead>
<tr>
<th>Five regions</th>
<th>Sofia City</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td></td>
</tr>
<tr>
<td>1992–94</td>
<td></td>
</tr>
<tr>
<td>1995–96</td>
<td></td>
</tr>
</tbody>
</table>

(1995-96) than during the first 3 years of the study (1992–94). During the 2-year period 1995–96, the rate in Sofia City (18.4/100 000 children 0–59 months of age) was substantially higher than that in the other five regions (11.0/100 000 children 0–59 months of age) (Table 3).

The average age-specific incidences of Hib meningitis were 6.6, 11.5 and 2.8 per 100 000 population aged 0–5 months, 6–23 months and 24–59 months, respectively. For the most affected age group of children <2 years of age in Sofia city during the years 1995–96, Hib incidence rate peaked at 37.6/100 000 population.

DISCUSSION

This retrospective survey was part of a WHO-funded population-based surveillance study of Hib meningitis in Bulgaria, aimed at assessing the local burden of Hib meningitis. The survey was planned to provide baseline information on the crude rates of bacterial and viral meningitis in children <5 years of age and on the significance of different organisms causing bacterial meningitis in the same age group.

Results indicate that, during the 5-year study period, childhood meningitis was primarily bacterial in origin, and the causative bacterial agent was successfully identified in nearly two-thirds of the cases. N. meningitidis and Hib were determined to be the leading causes of bacterial meningitis in Bulgarian children 0–59 months of age, accounting for 36% and 32% of bacteriologically confirmed cases. The peak incidence of Hib disease occurred in children aged 6–23 months. These findings are consistent with the results of studies performed during the 1970s and 1980s in industrialized countries to characterize the baseline epidemiology of Hib disease in the pre-vaccine era.1–6

However, the incidence of Hib meningitis estimated in our study is low compared to reports from northern and central European countries, where it was found to range from 22 to 43 per 100 000 before the widespread use of Hib vaccines.17–20 The incidence of Hib meningitis in Bulgaria is similar to the rates of 4–18 per 100 000 reported from several southern European and Mediterranean countries.21–25 In Japan, the estimated incidence rates in a retrospective study ranged by region from 3.4 to 9.9 per 100 000 children 0–4 years of age, with a mean of 4.7/100 000; the results from Japan appear to be nearly identical to our findings.26

There are several possible reasons for the relatively low incidence of Hib meningitis found in this study. First, Hib may have been under-detected because of inadequate techniques for isolation and identification in the period covered by this retrospective study. Our study indicates substantial region-to-region variation in the proportion of Hib meningitis, with regions most successful in culturing a bacterial isolate showing the highest proportion of Hib meningitis (Table 1).

Prescribing antibiotics before obtaining a CSF specimen is known to interfere with the recovery of
causative agents by culture. Since it is common practice to prescribe antibiotics for febrile infants and young children in Bulgaria, this may have also contributed to lower incidence rates of Hib meningitis in this study.

The past decade witnessed the introduction of Hib conjugate vaccine into routine childhood immunization. In the developed countries, Hib disease has been virtually eliminated in a few years since the introduction of the vaccine. Lessons learnt in the USA, Canada and Europe have clearly demonstrated that it would now be possible to prevent >90% of invasive Hib infections by routine immunization with the vaccine in early infancy. As only 8% of Hib meningitis cases in Bulgaria were found to occur before the age of 6 months, the majority of these severe, life-threatening conditions would be prevented by vaccination.

In conclusion, despite the weaknesses and limitations of this retrospective study, it is the first to demonstrate that Hib is one of the leading causes of childhood bacterial meningitis in Bulgaria, and that Hib is at least as important for the country as the endemic N. meningitidis. Data from this study have challenged the notion that Hib is not a major issue for the country. This has drawn the attention of medical professionals in Bulgaria to the need for further prospective assessment of the burden of Hib meningitis in Bulgaria as the next step towards the development of appropriate preventive strategies.

ACKNOWLEDGEMENTS

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REFERENCES