Case Report:

Haemophilus influenzae Serotype a Meningitis

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Abstract. This work describes a case of Haemophilus influenzae serotype a meningitis in Brazil, after almost a decade since the introduction of Haemophilus influenzae serotype b conjugate vaccine. Uncertainty about the replacement of H. influenzae serotypes as a cause of invasive diseases justifies continuous surveillance, coupled with investigations of carriage rates and requirements of chemoprophylaxis in contact persons.

Keywords: Haemophilus influenzae serotype b, Haemophilus influenzae serotype a, meningitis

Introduction

Haemophilus influenzae (Hi) is a Gram-negative pleomorphic bacillus that may present a polysaccharide capsule. Encapsulated strains may be differentiated into 6 serotypes (a to f) [1], of which H. influenzae serotype b (Hib) is the main cause of invasive diseases [2]. It is estimated that the bacillus causes >3 million cases of serious disease, mainly meningitis and pneumonia in children <5-yr-old, with approximately 386,000 deaths each year worldwide [2].

Invasive Hi diseases in children were almost exclusively caused by serotype b prior to the introduction of H. influenzae serotype b conjugate vaccine in several countries in 1988 and in 1999 in Brazil [3]. According to de Almeida et al [3], epidemiological data show that during the prevaccination period (from 1990 to 1999) in Brazil, the annual mean coefficients of incidence were 22.3 and 8.8/100,000 in children age <1 yr and from 1 to 4 yr, respectively. After the implementation of Hib vaccine in the regular immunization program, the incidence of Hib meningitis in Brazil was reduced significantly [4]. Although the vaccine brought great benefits due to the decrease in Hib meningitis, it was suspected that other serotypes and non-tybable strains (non-encapsulated) probably became more frequent in infectious processes [5,6].

This report describes a case of meningitis caused by Haemophilus influenzae serotype a (Hia) in southern Brazil, almost a decade after the introduction of Haemophilus influenzae serotype b conjugate vaccine.

Case Report

A 5-mo-old white girl, from Maringá, Paraná, Brazil, was hospitalized at the University Hospital of the State University of Maringá in June 2007. The child had been greatly irritable, crying excessively for 3 days, and running a fever of 39°C; one jet-like vomit was reported by her parents.

Laboratory data revealed cloudy cerebrospinal fluid (CSF) with 8,523 leukocytes/mm³, predominantly polymorphonuclear (95%), non-detectable glucose, and total protein 272 mg/dl. A Gram stain of CSF sediment revealed an abundance of Gram-negative bacilli. Bacterial antigen screening for group B streptococci, H. influenzae serotype b, Streptococcus pneumoniae, Neisseria meningitidis A, B, C, Y, W135, and Escherichia coli K1 was negative by agglutination tests (Pastorex meningitis test, Bio-Rad, Marnes-la-Coquette, ...
France). CSF cultured on chocolate agar and incubated at 35°C for 24 hr in 5% CO₂ showed Gram-negative bacilli growth that was identified as Hia by biochemical and serologic tests. An antimicrobial susceptibility test carried out by disk diffusion showed susceptibility to ampicillin, chloramphenicol, ceftriaxone, and trimethoprim-sulfamethoxazole. A β-lactamase test performed with a Cefinase disc test (BD BBL, Sparks, MD, USA) yielded a negative result [7].

The patient was treated with iv ceftriaxone (350 mg tid) and iv dexamethazone (0.25 mg qid). Sodium dipyrone was administered when fever was present. The patient was isolated for ... tract was carried out; an initial dose of iv phenobarbital (70 mg) was administered, with a 35 mg qd maintenance dose.

Although the Gram stain was negative by the 4th day, CSF cytological changes continued to be observed on the 29th day of hospitalization; 7 CSF collections were undertaken for cytological, biochemical, and microbiological tests, which revealed leukocytes and biochemical alterations (Table 1). On the 17th day of hospitalization, the patient had a tonic-clonic convulsion. Aspiration of the upper respiratory tract was carried out; an initial dose of iv phenobarbital (70 mg) was administered, with a 35 mg qd maintenance dose.

Although the Gram stain was negative by the 4th day, CSF cytological changes continued to be observed on the 29th day of hospitalization; chloramphenicol (175 mg qid) was added and maintained for 14 days. Owing to cytological alterations in CSF, ceftriaxone was replaced by ceftazidime (450 mg tid) plus gentamicin (56 mg qd) on the 45th day of hospitalization and maintained for 12 days.

Four skull tomographs and nuclear magnetic resonance (NMR) images were undertaken. Although the tomographs did not show any malformations, anatomical variations, and collections or abscesses, the NMRs revealed frontal and parietal saliencies consistent with an inflammatory process. Other tests, such as serology for Histoplasma capsulatum, Herpes simplex 1 and 2, HTLV 1 and 2, and PCR for tuberculosis in CSF, were carried out, showing negative results. Although determinations of total-CH50 complement and immunoglobulins (IgA, IgG, IgM, and IgE) were undertaken, only IgA and IgG showed slightly low levels.

After hospitalization for 65 days (including 57 days with and 8 without antibiotics) and recovery of good health, the patient was discharged from the Neurology Department without anticonvulsive drug therapy. Clinical follow-up has revealed good psychomotor development.

Table 1. Results of biochemical assays and microscopy of CSF in a patient with Haemophilus influenzae serotype a meningitis during hospitalization at the University Hospital of the State University of Maringá, Paraná, Brazil.

<table>
<thead>
<tr>
<th>Days of hospitalization</th>
<th>1</th>
<th>4</th>
<th>14</th>
<th>22</th>
<th>28</th>
<th>57</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (cells/mm³)</td>
<td>8,523</td>
<td>64</td>
<td>96</td>
<td>151</td>
<td>170</td>
<td>36</td>
<td>142</td>
</tr>
<tr>
<td>Polymorphonuclear cells</td>
<td>95%</td>
<td>32%</td>
<td>9%</td>
<td>40%</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Monomorphonuclear cells</td>
<td>5%</td>
<td>67%</td>
<td>91%</td>
<td>60%</td>
<td>95%</td>
<td>96%</td>
<td>97%</td>
</tr>
<tr>
<td>Total protein (mg/dl)</td>
<td>272</td>
<td>95</td>
<td>114</td>
<td>36</td>
<td>71</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>nd</td>
<td>38</td>
<td>40</td>
<td>53</td>
<td>35</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Gram stain</td>
<td>GNB</td>
<td>NVB</td>
<td>NVB</td>
<td>NVB</td>
<td>NVB</td>
<td>NVB</td>
<td>NVB</td>
</tr>
</tbody>
</table>

nd: non-detectable; GNB: Gram-negative bacilli; NVB: non-visualized bacteria.

Discussion

In the current case of Hia meningitis, no underlying illness or immunological deficiency was detected that would have predisposed the patient to such prolonged illness as described. Although a few reports have already been described in Brazil [8,9], ours is the first Hia invasive disease case in Maringá, Paraná, Brazil. The importance of the current case report is self-evident, especially in Brazil, where Hib vaccine coverage is high. Broad-coverage immunization with the tetravalent vaccine against diphtheria, tetanus, whooping cough, and Hib has reduced the incidence of Hib-caused invasive illnesses and the rate of nasopharyngeal colonization [8,10,11].

Our patient had not received the third dose of tetravalent vaccine, normally given in the sixth month. Ribeiro et al [8] reported Hia-caused meningitis in infants who had only received 2 or 3 doses of the tetravalent vaccine. Tetravalent vaccine fails to protect against infections caused by Hi serotypes other than b. Further studies are needed to see if that is coincidence. It would be interesting to monitor a possible trend of normal flora replacement and the appearance of other agents that could cause invasive diseases [12].

Some authors [8,13-17] have reported an increase in non-b H. influenzae nasopharyngeal colonization and invasive diseases since the introduction of Hib conjugate vaccine. In a recent study in northeastern Brazil, Ribeiro et al [9] reported that Hia-caused meningitis was a local and transitory phenomenon that occurred during the first years after Hib conjugate vaccine
introduction (from 0.01 to 0.14 cases per 100,000 population), but it was not observed in the following years, without any threat worldwide. In analyses of population-based studies and the relevant literature, WHO [2], Millar et al [18] and Ladhani et al [19] failed to find evidence of increased incidences of non-b H. influenzae-caused invasive diseases.

According to Bruce et al [20], there are several possible explanations for the high proportion of Hia diseases after the vaccine introduction. The authors suggest (a) an increase in Hia virulence, (b) a reduction in Hib colonization, which may lead to an opened ecologic niche for the colonization by other microorganisms, and finally, (c) that the reduction of Hib diseases may be highlighting the Hia cases. This last factor probably could explain the case reported here, considering that in our region, no Hia meningitis was previously reported after Hib vaccine implementation.

Lipsitch [21], based on a mathematical model, suggested that the extent and importance of serotype replacement (if it occurs) depend on such factors as vaccine coverage, differences in the colonization biology, and interactions among the bacterial types.

Although there is concern that Hia and other serotypes of Hi may be emerging as agents of meningitis and other invasive diseases, this possibility must be carefully evaluated to elucidate the risks of passing disease by carriage of these microorganisms [5]. Continuous monitoring for invasive diseases is mandatory, coupled with investigations of the number of carriers and of the need of chemoprophyaxis in contact persons [20].

The current authors emphasize the urgent need for more information about Hi serotypes. Clinical microbiology laboratories should identify Hi serotype profiles in order to clarify their clinical importance. The authors also stress the need for reevaluation of current immunization schedules and possible modifications of the Hib conjugate vaccine in order to protect against invasive disease caused by other Hi strains.

References


