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Invasive *Haemophilus influenzae* Serotype f Case Reports in Mazovia Province, Poland

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Abstract: After successful introduction of anti-*Haemophilus influenzae* (Hi) serotype b vaccination program in Poland, invasive non-b or nontypeable *H. influenzae* infections have been reported more frequently alike in other countries all over the world. In this paper, we report 2 cases of *H. influenzae* serotype f (Hif) meningitis with severe clinical presentations which are rarely seen in previously healthy children.

The first case is a 6-year-old girl who was admitted to pediatric ward with signs of meningitis. Laboratory tests confirmed bacteremic meningitis caused by Hif. The girl responded very well to administered treatment and recovered without any further complications. No underlying comorbidities were found. The second patient was a 4-year-old boy who, in course of Hif bacteremic meningitis, developed rapid septicemia and, despite aggressive treatment, died within a few hours of hospitalization. The child's past history was unremarkable.

By presenting these cases, we would like to remind clinicians that invasive non-b Hi infections can become fatal not only in the group of the youngest children or children with coexisting comorbidities, as most commonly reported in the worldwide literature. At the same time, we want to emphasize the legitimacy of constant monitoring Hi epidemiology in order to take accurate actions if necessary.

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Abbreviations: CSF = cerebrospinal fluid, Hi = *Haemophilus influenzae*, Hib = *Haemophilus influenzae* serotype b, Hie = *Haemophilus influenzae* serotype e, Hif = *Haemophilus influenzae* serotype f, MLST = multilocus sequence typing, NRCBM = National Reference Centre for Bacterial Meningitis, NTHi = nontypeable *Haemophilus influenzae*, ST = sequence type.

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INTRODUCTION

Haemophilus influenzae (Hi) is a strictly human pathogen and one of the most important etiologic agents of severe invasive infections, mainly in children under 5 years of age. This bacterium may cause meningitis, septicemia, epiglottitis and septic arthritis, as well as upper and lower respiratory tract infections. Isolates of this species can be noncapsulated (nontypeable: NT) or covered with a polysaccharide capsule (encapsulated, typeable). Encapsulated isolates are divided into 6 serotypes, designated a to f based on their antigenic and structural diversity. Nontypeable Hi commonly colonize the upper respiratory tract and are responsible for recurrent respiratory infections (acute otitis media, acute bacterial rhinosinusitis, and exacerbation of chronic respiratory diseases) in all age groups. For years, *H. influenzae* serotype b (Hib) was a serotype most commonly associated with severe invasive infections. Routine immunization against Hib, however, dramatically reduced the number of Hib cases, especially in children under 5 years of age. At the same time, invasive infections caused by NTHi, *H. influenzae* serotype f (Hif) and other serotypes have been reported more frequently.[1,2] Mostly they have occurred among toddlers, older people and patients with coexisting comorbidities, fatal outcomes have been relatively rare.[1,3,4,5]

We present 2 cases of Hif meningitis in children that occurred in Warsaw and suburbs between 2013 and 2014. Described patients were 4 and 6 years old, were fully immunized against Hib and previously healthy, and while one of them recovered uneventfully, other one died unexpectedly shortly after the onset of infection.

The ethical approval and patients' consent for this study were not necessary as it did not involve any experimental treatment, invasive diagnostics, and does not reveal any confidential information about patients that could violate their privacy.

CASE REPORTS

Patient A is a 6-year-old girl with a history of adenoid and tonsillar hypertrophy, admitted to a local hospital in March 2013 with clinical signs of meningitis. Before admission, she presented with a 2-days' history of fever (39 °C), vomiting, abdominal and ear pain. In Emergency Department, she was lethargic, but her vital signs remained normal. Examination revealed left otitis media, moderate dehydration, tonsillar hypertrophy, neck rigidity (2 cm), and positive Brudzinski neck sign. Cerebrospinal fluid (CSF) analysis showed pleocytosis of 311/mm^3 white blood cells with 90% neutrophils, protein 220.1 mg/dL and glucose 50.6 mg/dL (24% of serum glucose level). An empirical treatment with cefotaxime, vancomycin, and dexamethasone was administered. After several days, CSF and blood cultures revealed Hi susceptible to cefotaxime; therefore, single-drug treatment with cefotaxime was continued for 14 days. Fever resolved within 24 hours of intravenous

antibiotic administration and the child's neurological status improved after 3 days. During hospitalization, primary and acquired immunodeficiency diseases were ruled out, and the girl was discharged from the hospital after returning to her baseline state of health.

Patient B was a 4-year-old boy without previous medical records, who was brought to the hospital by emergency ambulance with signs of septicemia in September 2014. Before admission, he presented with 1-day fever (>39 °C), vomiting, and diarrhea. In Emergency Department, the patient's condition was serious; he demonstrated generalized petechial rash, severe dehydration, positive Brudzinski neck sign, low blood pressure, inspiratory and expiratory dyspnea. Laboratory evaluation revealed: white blood cells count of 1030/mm^3, thrombocytopenia of 49,000/mm^3, hemoglobin 9.5 g/dL, C-reactive protein of 10 mg/dL (normal <1.0 mg/dL), procalcitonin 61.7 ng/dL (normal <0.05 ng/dL), lactic acid 9.4 mmol/l (0.5–2.2 mmol/l), increased INR (international normalized ratio of prothrombin time) up to 3.08, activated partial thromboplastin time 100 seconds, D-dimers >35,000 μg/L. Cerebrospinal fluid was not obtained in spite of several attempts. An empirical treatment with ceftriaxone and vancomycin was administered. Due to rapidly developing symptoms of heart failure and respiratory distress, the patient was transferred to the Intensive Care Unit. Despite aggressive treatment, the boy died a few hours later. The clinical picture strongly suggested a meningococcal septicemia, whereas, unexpectedly, postmortem the patient's blood cultures grew Hi. Family history was unremarkable except for the fact that the boy's uncle died in adolescence due to septicemia. The importance of that fact, however, remains unclear, as the family refused further medical investigation.

The Hi isolates from both cases were sent to the National Reference Centre for Bacterial Meningitis (NRCBM) for further analysis. They were identified as Hi serotype f by polymerase chain reaction. Minimal inhibitory concentrations of ampicillin and chloramphenicol were 0.25 μg/mL and 1 μg/mL (Patient A isolate), 0.38 μg/mL and 1.5 μg/mL (Patient B isolate) respectively, and for both isolates minimal inhibitory concentration of cefotaxime was 0.03 μg/mL and of meropenem 0.047 μg/mL. By multilocus sequence typing (MLST), both isolates were identified as sequence type 124 (ST 124),[6] (www.mlst.net).

DISCUSSION

We present 2 cases of Hif meningitis with radically different courses of infection. The reason for the fatal infection outcome in patient B remains unclear, making his case very alarming. Both patients were previously healthy, were not asplenic, they received all 4 doses of anti-Hib vaccination, and to our best knowledge, had no contact with anybody contagiously ill. Both Hif isolates were susceptible to commonly used antibiotics and caused bacteremic meningitis in both children, yet septicemia developed only in the boy's case (patient B). The isolates may have had an unidentified diversity of virulence, but it cannot be confirmed. The majority of authors point out that the most susceptible to invasive non-Hib infections are individuals at both extremes of age and with potential comorbidities, resulting in diverse severity of infection.[1,3,4,5] Discrepancies between non-Hib serotypes have also been observed—for instance, Hif infections are associated with a higher incidence but lower case fatality rate in comparison to *H. influenzae* serotype e (Hie).[1,3] One of the possible explanations suggests that Hie is less pathogenic than Hif and usually infects older people or those who are chronically ill or immunosuppressed and therefore more likely to die. Consequently, in general, patients with Hif infections recovered uneventfully, while those with Hie infections either died or developed further complications.[1] We find patient's B fatal case, as well as the fatal Hif septicemia case reported by Zacharisen et al[7] in an otherwise healthy 4-year-old girl without underlying predisposing conditions to be in opposition to these observations. Although undetected immunodeficiency cannot be excluded, these 2 cases are bothering, as symptoms of infection were very acute in nature and the outcome rapidly fatal. Therefore, in the face of the gradual increase of Hif infections, further continuous monitoring of invasive Hi diseases is certainly required.[1,2,4]

An international surveillance study performed in Europe in 1996 to 2006 showed that the dominant serotypes in invasive infections caused by non-b Hi were Hif and Hie; however, the study did not reveal any significant change in Hif incidence in particular.[3] According to more recent data from England and Wales, over 10 years (2001–2010), there was an 11% increase in Hif incidence year-on-year and a 7.4% increase in Hie incidence; in 2009 Hif incidence exceeded that of Hib.[1]

In Poland, mass vaccination against Hib started in 2007. Before that, according to data confirmed by the NRCBM, Hib was responsible for 97% cases of Hi invasive diseases in Polish children under 5 years of age[8] (NRCBM unpublished data). Despite the decrease in Hib incidence after 2007 (in 2014 the NRCBM reported only 1 Hib case in an adult patient), the total number of invasive Hi infections isolates obtained by the NRCBM has not changed. Instead, a shift in patients' age toward older age as well as an increase in infections caused by NTHi and non-b serotypes has been observed. In the post-vaccination period (2008–2014), out of 181 isolates reported, only 41 (23%) were of serotype b, 8 of serotype f (4%), 1 of serotype e (1%), and the other 131 isolates were NTHi (72%). Multilocus sequence typing analysis of all 10 Polish Hif isolates identified all of them but 1 as sequence type 124, a predominant ST among invasive Hif isolates worldwide, found also during our study[1,5,9] (NRCBM unpublished data, 2015). It should be, however, noted that invasive Hi diseases surveillance in Poland is highly affected by the insufficient frequency of blood culturing, which is a consequence of low adherence to recommendations concerning blood cultures, and results in an obvious underestimation of the true incidence of invasive Hi infections.

An analysis of invasive Hi cases in children between 0 and 10 years of age in Mazovia province has revealed that all 43 cases reported prior to 2007 were meningitis caused by Hib (until 2005 only meningitis Hi cases were reported). The situation started to change in 2007, after the introduction of routine vaccination. Between 2008 and 2014, the NRCBM reported 16 cases of Hi in the specified age group and territory. The majority of cases were presented as septicemia (56%), followed by meningitis (37%) and 1 case of bacteremic pneumonia. Nontypeable Hi were responsible for 50% of infections, followed by Hib (38%) and Hif (12%: 2 cases presented above) (Figure 1) (NRCBM unpublished data, 2015). As mentioned before, low and underestimated number of invasive Hi cases notified annually by surveillance system in Poland is the limitation of this data. Despite that, the general findings are consistent with the trends in invasive Hi epidemiology reported for Europe.[1,3]

The cases presented are alarming and should make the practitioner aware that Hif isolates are capable of causing septicemia and meningitis in otherwise healthy children with a possible fatal outcome. All of invasive Hi cases, including Hif, should be obligatorily reported, and responsible isolates should

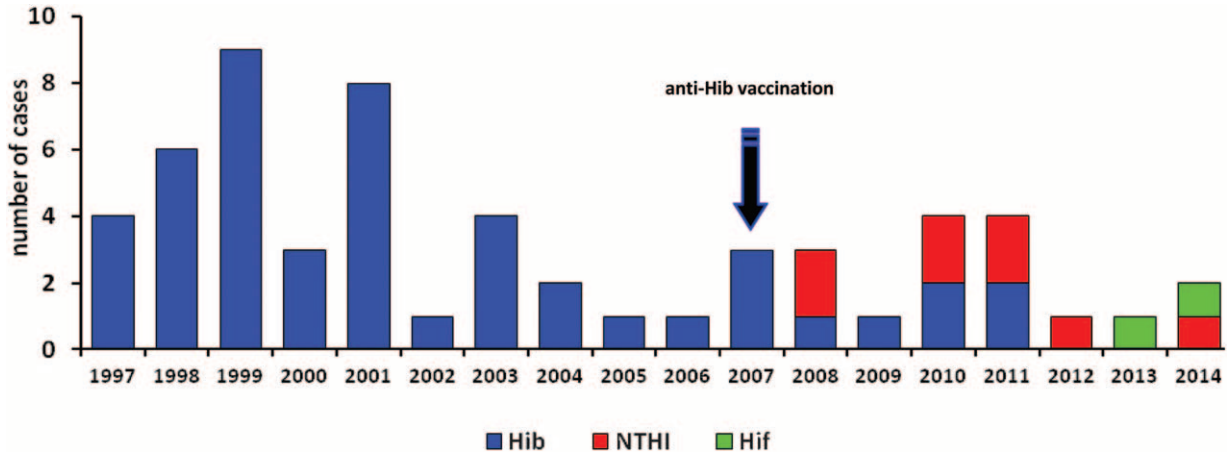

FIGURE 1. Serotype distribution among *Haemophilus influenzae* isolates responsible for invasive infections in children below 10 years of age in Mazovia province, 1997 to 2014 (National Reference Centre for Bacterial Meningitis data).

be examined in reference laboratories by susceptibility testing, serotyping, and MLST analysis. That will provide the most reliable information about the current epidemiology of Hi and may be helpful in the selection of proper empiric treatment. If there is a continuous and significant increase in non-Hib invasive infections, one may consider the possibility of introducing a recommendation for an adequate chemoprophylaxis after contact with, for example, Hif cases or even developing a new vaccine.

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