A case of acute epiglottitis caused by *Haemophilus influenzae* type a in an adult

Ashley M. Cerqueira,1 Raymond S. W. Tsang,2 Frances B. Jamieson3,4 and Marina Ulanova1,5

1Lakehead University, Thunder Bay, Ontario, Canada
2Vaccine Preventable Bacterial Diseases, National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba, Canada
3Public Health Laboratories, Public Health Ontario, Toronto, Ontario, Canada
4Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Canada
5Northern Ontario School of Medicine, Thunder Bay, Ontario, Canada

**Introduction:** Prior to the introduction of a paediatric conjugate vaccine in the early 1990s, *Haemophilus influenzae* serotype b (Hib) was a major cause of childhood meningitis and pneumonia. Since becoming part of national immunization programmes, the Hib conjugate vaccine has been very successful in preventing invasive Hib disease worldwide. However, in the post-Hib vaccine era, the emergence of invasive disease caused by non-type b *H. influenzae* has been reported from several countries. Previous studies by our group found an increased incidence of invasive disease caused by *H. influenzae* serotype a in Northwestern Ontario, Canada, during 2002–2011. Most of the cases of invasive *H. influenzae* type a disease occurred in young children.

**Case presentation:** Our continued surveillance identified a case of epiglottitis caused by *H. influenzae* type a in a 65-year old woman. This life-threatening condition was historically associated with invasive Hib disease in young children but had not previously been reported in association with *H. influenzae* type a. We describe the clinical presentation of this case as well as characteristics of the *H. influenzae* type a isolate.

**Conclusion:** Our findings stress the importance of continued surveillance of *H. influenzae* in the post Hib-vaccine era, and point to the significance of *H. influenzae* type a as a cause of severe invasive disease in countries with a universal paediatric anti-Hib immunization programme.

**Keywords:** epiglottitis; *Haemophilus influenzae*.

**Introduction**

*Haemophilus influenzae* is a Gram-negative coccobacillus, which can be asymptomatically carried in the nasopharynx, but is also capable of causing invasive or local infections, including otitis media, sinusitis, pericarditis, urinary tract infections, septicaemia, septic arthritis, meningitis, pneumonia and epiglottitis (Pittman, 1931; Wenger, 1998). Many *H. influenzae* strains carry antigenically distinct polysaccharide capsules and are correspondingly divided into six serotypes (a–f), while the unencapsulated strains are termed non-typeable (NTHi) (Pittman, 1931).

The most virulent serotype of *H. influenzae* is serotype b (Hib), followed by type a (Zwahlen *et al.*, 1989). Before the introduction of the Hib conjugate vaccine at the beginning of the 1990s, Hib was the predominant cause of bacterial meningitis and invasive disease in children, with 30 % of all invasive *H. influenzae* infections resulting in epiglottitis (Wenger, 1998). A severe, life-threatening condition, epiglottitis can have a rapid onset and may present in adults as fever, drooling and dyspnoea related to oedema and inflammation of the epiglottis (Frantz *et al.*, 1994; Senior *et al.*, 1994). In the post-vaccine era, *H. influenzae* is still an important cause of epiglottitis, affecting children primarily under the age of 5 years (Table 1) (Chalmers, 2010; Chandler *et al.*, 2009; Charuvanij & Houghton, 2009; Hopkins *et al.*, 2006; Jiang *et al.*, 2003; Rogers *et al.*, 2010; Salamanca Santamaria *et al.*, 2011; Tanner *et al.*, 2002).

During the last decade, an increased prevalence of non-Hib strains in the aetiology of invasive *H. influenzae* disease has been reported in countries with universal paediatric immunization against Hib, including Canada (Adam *et al.*...
Table 1. Recent cases of invasive *H. influenzae* disease causing epiglottitis

<table>
<thead>
<tr>
<th>Location</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Bacteria characteristics</th>
<th>Clinical presentation</th>
<th>Disease outcome</th>
<th>Underlying conditions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>2</td>
<td>F</td>
<td><em>H. influenzae</em> type b</td>
<td>Epiglottitis</td>
<td>Infection cleared</td>
<td>None</td>
<td>Tanner <em>et al.</em> (2002)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>F</td>
<td><em>H. influenzae</em> type b</td>
<td>Epiglottitis</td>
<td>Infection cleared</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>M</td>
<td><em>H. influenzae</em> type b</td>
<td>Epiglottitis</td>
<td>Infection cleared</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Detroit, US</td>
<td>3</td>
<td>M</td>
<td><em>H. influenzae</em> type f</td>
<td>Epiglottitis</td>
<td>Infection cleared</td>
<td>None</td>
<td>Aravapalli &amp; Sahai (2013)</td>
</tr>
<tr>
<td>Dumfries, UK</td>
<td>4</td>
<td>F</td>
<td><em>H. influenzae</em> type b</td>
<td>Epiglottitis</td>
<td>Infection cleared</td>
<td>None</td>
<td>Chandler <em>et al.</em> (2009)</td>
</tr>
<tr>
<td>Madrid, Spain</td>
<td>4</td>
<td>M</td>
<td><em>H. influenzae</em> type b</td>
<td>Epiglottitis</td>
<td>Expired</td>
<td>None</td>
<td>Salamanca Santamaria <em>et al.</em> (2011)</td>
</tr>
<tr>
<td>New Taipei City, Taiwan</td>
<td>4</td>
<td>M</td>
<td><em>H. influenzae</em> type b</td>
<td>Epiglottitis</td>
<td>Infection cleared</td>
<td>None</td>
<td>Jiang <em>et al.</em> (2003)</td>
</tr>
<tr>
<td>Vancouver, Canada</td>
<td>5</td>
<td>F</td>
<td><em>H. influenzae</em> type f</td>
<td>Epiglottitis</td>
<td>Infection cleared</td>
<td>Multi-organ system dysfunction, acute renal failure, hypertension, systemic lupus erythematosus</td>
<td>Charuvanij &amp; Houghton (2009)</td>
</tr>
<tr>
<td>Kilmarnock, UK</td>
<td>64</td>
<td>F</td>
<td><em>H. influenzae</em> type b</td>
<td>Epiglottitis, necrotizing fasciitis</td>
<td>Infection cleared</td>
<td>Hypertension, osteoarthritis</td>
<td>Chalmers (2010)</td>
</tr>
</tbody>
</table>
a case of acute epiglottitis caused by Haemophilus influenzae type a in an adult

al., 2010; Bruce et al., 2008; Ladhani et al., 2010). Recent surveillance of invasive H. influenzae disease in Northwestern Ontario (Canada) identified 50 cases between January 2002 and July 2011 (Brown et al., 2009; Sadeghi-Aval et al., 2013). Of the 40 cases with available serotype information, 18 (45 %) were due to H. influenzae type a and occurred mostly in young children (Brown et al., 2009; Kelly et al., 2011; Sadeghi-Aval et al., 2013). Our continued surveillance between August 2011 and October 2012 identified one more case of invasive H. influenzae type a disease, i.e. acute epiglottitis in an adult. To the best of our knowledge, this is the first reported case of epiglottitis due to H. influenzae type a infection.

Case report
A previously well 65-year-old woman presented to a local walk-in clinic with sore throat, fever, chills and general malaise. Previous medical history was significant for obesity, diabetes mellitus type 2, hyperlipidaemia and proteinuria, and osteoarthritis. She was prescribed Tamiflu at the clinic, but returned the following day with progressive dysphagia and dyspnoea, decreased appetite, severe sore throat, increased neck swelling and drooling. She also reported a feeling that her throat was closing and was immediately referred to the emergency department.

Upon physical examination she was alert and had a temperature of 35.6 °C, a heart rate of 98 min⁻¹, a blood pressure of 113/60 mmHg, a respiratory rate of 18 min⁻¹, and a blood oxygen saturation of 100 % on oxygen therapy. Cervical lymphadenopathy with tenderness on palpation was noted. Physical examination revealed no other significant signs. The patient had a white blood cell count of 11.0 × 10⁹ L⁻¹ (86 % neutrophils, 6 % lymphocytes, 8 % monocytes) and a platelet count of 148 × 10⁹ L⁻¹. Examination of arterial blood gases indicated a pH of 7.43 (normal 7.35–7.45), PaCO₂ of 31 mmHg (normal 35–45 mmHg), PaO₂ of 199 mmHg (normal 80–100 mmHg), HCO₃⁻ (bicarbonate) of 21 mEq L⁻¹ (normal 22–26 mEq L⁻¹). Chest X-ray revealed clear lungs, normal pleura and a normal-sized heart. Neck X-ray showed prominence of the epiglottis and upper tracheal narrowing, confirming epiglottitis (Fig. 1). Based on these findings, she was started on intravenous dexamethasone 10 mg, ceftriaxone 1 g and vancomycin 1 g. In response to treatment, her pharyngeal oedema quickly decreased, her breathing eased, and a tracheotomy was not required. Three days after admission, the patient showed an improvement in breathing and swallowing, and was able to speak. She was placed on oral Keflex for 5 days and discharged home.

Investigations
Identification and biotyping of H. influenzae was accomplished by standard biochemical tests (Kilian, 2003), and confirmed by 16S rRNA sequencing (Lau et al., 2004).

Fig. 1. Neck radiograph indicating epiglottitis.

Serotyping was done by both bacterial agglutination test (using antisera from Difco Diagnostics) and PCR to detect the serotype-specific genes according to the procedure described by Falla et al. (1994). Clonal analysis of H. influenzae isolates was done by multilocus sequencing typing (MLST) (Meats et al., 2003). Detection of the IS1016-bexA partial deletion in the capsule locus was done by PCR (Kroll et al., 1994). Detection of β-lactamase production in H. influenzae was carried out using DrySlide Nitrocefin (BBL; Becton Dickinson). Antimicrobial susceptibility testing was done by the disk diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2011).

Characteristics of the pathogen
Blood culture was positive for H. influenzae. Serotyping by slide agglutination indicated H. influenzae type a, which was confirmed by detection of serotype-specific capsular polysaccharide synthesis genes. The characteristics of this isolate together with other invasive H. influenzae type a isolates from Ontario, Canada are presented in Table 2. The majority of invasive H. influenzae type a isolates (including this epiglottitis isolate) in Ontario and other Canadian provinces (Tsang et al., 2013) belonged to ST-23 and showed similar characteristics.

Discussion
The use of Hib conjugate vaccines has substantially decreased the incidence of invasive Hib disease worldwide (Wenger, 1998). In the pre-vaccine era incidence rates of invasive Hib among children <5 years old in the USA were
between 40 and 100 per 100 000 (Wenger, 1998), while in the post-vaccine era the incidence rates had fallen to 0.21 per 100 000 in 2006 (Morris et al., 2008). However, Hib vaccine is highly specific and it does not confer protection against other H. influenzae serotypes. Moreover, as paediatric immunization results in decreased nasopharyngeal carriage of Hib in populations with high vaccine coverage (McVernon et al., 2004; Takala et al., 1991), this may potentially allow non-type b serotypes to occupy its ecological niche (Lipsitch, 1997). An increase in prevalence of non-type b H. influenzae in the post-Hib vaccine era has been documented in North America and Europe, where the majority of invasive H. influenzae infections are now due to NTHi, followed by serotype f (Adam et al., 2010; Ladhani et al., 2010; Tsang, 2008). However, current epidemiological studies in Alaska and some regions of Canada, particularly in northern communities with predominantly aboriginal populations, indicate an increase in prevalence of invasive H. influenzae disease caused by serotype a (Brown et al., 2009; Bruce et al., 2008, 2013; Kelly et al., 2011; Rotondo et al., 2013; Tsang et al., 2007; Ulanova, 2013; Ulanova & Tsang, 2014). Because surveillance of non-Hib H. influenzae, including H. influenzae type a, prior to the introduction of Hib vaccination was incomplete it is difficult to determine if the increase in non-type b cases is due to serotype replacement or improved surveillance. It remains controversial whether serotype replacement occurs in the post-Hib vaccine era. In Alaska, no cases of invasive H. influenzae type a disease were reported before 2002, but since then the incidence rates have been increasing and outbreaks have occurred (Bruce et al., 2013). In contrast, while the incidence of H. influenzae type a meningitis in Brazil increased eight-fold in the first year after the introduction of Hib vaccination (Ribeiro et al., 2003), no increase was observed during the following 4 years of surveillance (Ribeiro et al., 2007).

To the best of our knowledge, H. influenzae type a has not previously been reported as a cause of epiglottitis. However, as Hib was the dominant cause of invasive H. influenzae disease in the pre-vaccine era, some cases of epiglottitis caused by other serotypes might have been overlooked. In Canada, invasive non-Hib disease was not included in the national notifiable disease list until 2007 although invasive Hib has been reportable since 1986 (PHAC, 2012). Invasive non-Hib is not currently reportable in Ontario.

The capsular polysaccharide is an important virulence factor responsible for serious infections caused by encapsulated bacterial pathogens such as H. influenzae and Streptococcus pneumoniae. Capsule protects the bacteria against complement-mediated killing and phagocytosis, the essential immune protective mechanism. H. influenzae can be divided into three groups based on polysaccharide structure and resistance to complement-mediated killing: Hib and H. influenzae type a are the most virulent serotypes and are composed of a neutral sugar, an alcohol (ribitol) and a phosphodiester; serotypes c and f are less virulent and less resistant to complement attack, and are composed of an N-acetylated amino sugar, a second saccharide, and a phosphodiester; serotypes d and e are rapidly lysed by complement and have a repeat unit of an N-acetylglicosamine and N-acetylmannosamine uronic acid (Sutton et al., 1982; Zwahlen et al., 1989).

Most Hib strains contain a duplication of the cap locus flanked by an insertion sequence (IS1016) and belong to clonal division I, while a small subpopulation of Hib and all serotype f strains belong to clonal division II (Kroll et al., 1991; Sill et al., 2007). Similar to Hib, H. influenzae type a can be divided into two clonal divisions, with most Canadian invasive serotype a isolates belonging to clonal division I and the ST-23 clonal complex (Tsang et al., 2013). Transformation studies suggest that changes to the cap locus, in particular the serotype-specific genes (Kroll et al., 1990), directly alter the virulence of H. influenzae (Zwahlen et al., 1989). Moreover, clusters of invasive H. influenzae type containing the partial deletion of IS1016-bexA are associated with poorer clinical outcomes, potentially due to amplification of the capsule loci, leading to enhanced production of capsular polysaccharide and decreased host immune response (Lima et al., 2010).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Epiglottitis Hia*</th>
<th>Other invasive Hia* (no. of isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of case isolates</td>
<td>1</td>
<td>(24)</td>
</tr>
<tr>
<td>ST by MLST/biotype</td>
<td>ST-23/biotype II</td>
<td>ST-23/biotype II (20)</td>
</tr>
<tr>
<td>Partial IS1016-bexA deletion</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>β-lactamase</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Antibiotic susceptibility</td>
<td>Uniformly sensitive†</td>
<td>Uniformly sensitive†</td>
</tr>
</tbody>
</table>

*H. influenzae serotype a. †Susceptible to ampicillin, amoxicillin-clavulanic acid, cefaclor, ceftriaxone, chloramphenicol, tetracycline, azithromycin, clarithromycin, trimethoprim–sulfamethoxazole, ciprofloxacin, levofloxacin, meropenem and imipenem.
H. influenzae strains can be characterized on the basis of their MLST profile, which can help identify capsule switching among isolates (Sill et al., 2007). In previous reports, we stated that H. influenzae type a isolates from cases in northern Ontario belonged to a clonal complex defined by ST-23 and two related STs (ST-56 and ST-929) with one or two housekeeping gene alleles different from ST-23 (Kelly et al., 2011; Sadeghi-Aval et al., 2013). In the present case of epiglottitis caused by H. influenzae type a, the isolate belonged to ST-23, confirming the prevalence of this genotype in two neighbouring Canadian provinces (Manitoba and Ontario) (Sadeghi-Aval et al., 2013; Sill et al., 2007). In agreement with our previous findings in northern Ontario and Manitoba (Kelly et al., 2011; Tsang et al., 2006), the H. influenzae type a isolate reported here did not contain the IS1016-bexA partial deletion. Similar to our previous findings (Kelly et al., 2011; Sadeghi-Aval et al., 2013), the isolate was sensitive to all tested antibiotics including one used for treatment (ceftriaxone), contributing to the rapid therapeutic response. The patient was also put on steroids, which might have significantly helped to reduce the epiglottal oedema.

Conclusion

The case of epiglottitis in an adult caused by H. influenzae type a illustrates dynamic changes in the epidemiology of invasive H. influenzae disease in the post-Hib vaccine era. Given similarities in virulence between H. influenzae type a and Hib strains and continuing vaccine pressure in countries with universal paediatric anti-Hib immunization, the serotype a may become more prevalent and cause clinical presentation similar to invasive Hib disease in the pre-vaccine era. This emphasizes the importance of continued global surveillance of all H. influenzae strains for the development of health promotion strategies, as well as for research exploring pathogen–host interactions and a universal vaccine against all serotypes of H. influenzae.

Acknowledgements

The authors thank Wendy Gouliquer for her help in identifying invasive H. influenzae cases; Mieke DeRoover, Cynthia Boegh and Judy Clarke for their assistance in obtaining the patient medical charts; and Michelle Shuel and Dennis Law for technical assistance. Clinical data were collected from the Thunder Bay Regional Health Sciences Center (TBRHSC) in Northwestern Ontario, where the hospital charts of the cases were reviewed retrospectively. The research ethics boards of both TBRHSC and Lakehead University had previously approved this work. The authors declare that no conflict of interest exists.

References


Haemophilus influenzae

Infect Immun

JMM Case Reports

Global epidemiology of invasive Haemophilus influenzae

Int J Clin Microbiol


