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Recurrent invasive *Haemophilus influenzae* serotype a infection in an infant

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Abstract

Background: Before introduction of conjugated *Haemophilus influenzae* serotype b (Hib) vaccines into the routine childhood immunization programs, Hib was a major cause of meningitis in infants and children under the age of 5. In the post-Hib vaccine era, the epidemiology of invasive *H. influenzae* has changed substantially with most invasive diseases now caused by non-Hib strains, including *H. influenzae* serotype a (Hia) and serotype f, as well as non-encapsulated or non-typeable strains. This case report describes the microbiology of Hia in a recurrent invasive infection in an infant. The Hia strain involved is described together with current knowledge of Hia infection including methods of protection.

Methods: Isolates were characterised by Gram stain, growth factor requirements, biotype, serotype, detection of *IS*1016-*bexA* deletion, multilocus sequence typing, pulsed-field gel electrophoresis and antimicrobial susceptibility testing.

Results: All three isolates appeared to be identical, belonged to biotype II, serotype a, sequence type 23, lacked the *IS*1016-*bexA* partial deletion, and were susceptible to commonly prescribed antibiotics tested.

Conclusion: Hia has emerged as a significant invasive pathogen in the post Hib vaccine era. MLST and PFGE serve as useful techniques for typing of Hia. Many attributes of Hia and the disease it causes bear resemblance to Hib and Hib disease, including the ability to cause recurrent infections. This raises the potential for protection by vaccination and chemoprophylaxis.

Keywords: *Haemophilus influenzae*, serotype a, recurrent infection, Hib

Introduction

Haemophilus influenzae is responsible for causing a number of invasive (meningitis, septicemia, septic arthritis, etc.) and non-invasive (otitis media, bronchitis, sinusitis, etc.) infections. *H. influenzae* isolates may or may not produce a polysaccharide capsule and are designated as encapsulated, or non-encapsulated, respectively. Encapsulated strains can be further characterized as belonging to one of serotypes a, b, c, d, e, or f based on their capsular structure, and non-encapsulated strains are designated as non-typeable.

A conjugate Hib vaccine was developed and introduced into the routine immunization schedule in many countries, including Canada in the early 1990s. Decreased instance of Hib disease has since been observed [1], permitting other serotypes and non-typeable strains to become more prevalent in some regions, as indicated by routine surveillance.

Here we report a case of recurrent invasive infection in an infant due to Hia. We characterized the strains isolated from the infant during the two episodes of infection, and we discussed our current knowledge of Hia infection together with potential methods of protection.

Case presentation

We report a case of recurrent invasive *Haemophilus influenzae* serotype a (Hia) infection in a 10-month old native infant in Saskatchewan, Canada. The infant's mother was infected with both the human immunodeficiency virus (HIV) and hepatitis C virus (HCV), and as such the infant received Azidothymidine (AZT) at birth and during infancy as per national guidelines [2]. In November 2013, the patient was admitted to hospital with

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blood culture confirmed diagnosis of Hia septicemia which was successfully treated with a standard antibiotic regime [3] to which the strain was fully susceptible. The patient was discharged without any significant sequelae from the Hia infection. However, the infant was re-admitted to the hospital in February 2014 with suspected sepsis and meningitis, and both CSF and blood cultures grew Hia. Despite vigorous treatment with antibiotics, the infant succumbed to the second episode of the Hia infection. At both admissions to the hospital, the patient remained HIV and HCV negative by PCR detection of the viruses. We believe this case is of interest because it demonstrates how Hia resembles Hib in the pre-Hib vaccine era, in potentially causing severe recurrent systemic infections. The resemblance of Hia to Hib may raise the possibility of potential control through chemoprophylaxis and ultimately development of a Hia conjugate vaccine.

Investigations

Identification was based on Gram stain morphology, growth requirement for X and V factors, and standard biochemical tests [4]. Biotyping was determined by biochemical reactions for urease, indole and ornithine decarboxylase [5]. Serotype was determined by the slide agglutination method using commercial antisera (Difco, Becton Dickinson, Oakville, Ontario, Canada), and confirmed by PCR amplification of serotype specific and capsule transport, *bexA*, genes [6]. Detection of deletion involving parts of the *IS*1016 and *bexA* genes in the capsule synthesis operon was done as previously described [7].

For multilocus sequence typing (MLST), 7 housekeeping genes (*adk*, *atpG*, *frdB*, *fucK*, *mdh*, *pgi*, *recA*) were amplified by PCR and sequenced as previously described [8]. The MLST website (http://haemophilus.mlst.net) was used to assign allele numbers and sequence types. For pulsed-field gel electrophoresis (PFGE), cultures were suspended in 100 mM Tris-EDTA buffer and adjusted to a turbidity of 0.5. The suspension was mixed with 1.5% SeaKem Gold Agarose (Lonza, Cedarlane, Burlington, North Carolina, USA), to form plugs. The plugs were treated with lysis buffer and washed to yield genomic DNA free from any residual reagents. Plug slices were digested with *SmaI* restriction enzyme (Invitrogen, Burlington, Ontario, Canada) and PFGE was performed using the CHEF-DR III unit (Bio-Rad Laboratories, Mississauga, Ontario, Canada). Besides the isolates from the current case, other Hia described in our previous study [9] were included for comparison.

Antibiotic susceptibility disk diffusion testing was conducted according to CLSI guidelines [10], and β-lactamase production was determined using DrySlide Nitrocefin (Becton Dickinson, Oakville, Ontario, Canada).

Characterization of the Hia isolated from this case

The blood culture isolate from the first hospitalization and the isolates from the blood and CSF cultures from the second hospitalization three months later were identified as biotype II *H. influenzae*. Slide agglutination with serotyping antisera revealed all three isolates as serotype a, and they were confirmed to contain the *bexA* and the serotype a-specific genes by PCR. MLST revealed all three isolates belonging to ST-23. They lacked the *IS*1016-*bexA* partial deletion in their capsule synthesis (*cps)* operon. All three isolates did not produce β-lactamases, and were susceptible to ampicillin, amoxicillin-clavulanic acid, cefaclor, ceftriaxone, chloramphenicol, tetracycline, azithromycin, clarithromycin, ciprofloxacin, moxifloxacin, levofloxacin, imipenem, meropenem, and trimethoprim-sulfamethoxazole. PFGE also showed identical DNA fingerprints for the three Hia isolates (**Figure 1**).

Discussion

The capsule of Hia is most similar to Hib but very different from capsules of the other serotypes. Hia capsule is made up of a polymer of a di-saccharide of glucose-ribitol phosphate [11] while the polymer of Hib capsule is ribose-ribitol phosphate [12]. Experimental studies in animals using isogenic mutants that differ from each other by their capsule structures reveal that Hib is the most virulent serotype followed by Hia, and then other serotypes [13].

In this case of a recurrent Hia systemic infection, although the bacteria isolated from the patient at the hospital during both episodes of infection were identical, the clinical findings suggested that it was likely a re-infection rather than relapse. First the isolates involved were highly sensitive to the antibiotics tested as well as to the antibiotic used to

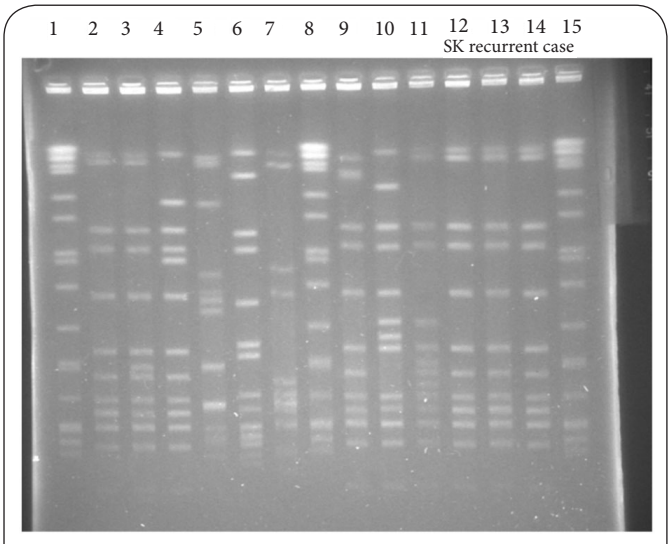

Figure 1. Pulsed-field gel electrophoresis of *Haemophilus influenzae* strains, comparing DNA fingerprints from isolates obtained from the recurrent case in Saskatchewan (SK) with *H. influenzae* strains representing different Sequence Type (ST). Lanes 1, 8 and 15 were profiles from *Salmonella braenderup* as markers; Lanes 12, 13 and 14 were profiles from *H. influenzae* serotype a isolates of the recurrent case. Lanes 2, 3, 4 and 11, ST-23; Lane 5, ST-372; Lane 6, ST-4; Lane 7 ST-62; Lane 9, ST-56, Lane 10, ST-529.

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treat the initial episode of the infection. The patient fully recovered, and was discharged without any noted abnormality. Secondly, the patient appeared well during the three month period between the infections. The fact that all three strains recovered from the patient in the two episodes of infection were identical merely reflected the common nature of this clone of Hia in Canada [9].

Indeed, of the 116 Hia isolates collected from 1995-2012 at the NML from Canadian sources, 95 (82%) belonged to ST-23, and another 19 (16%) belonged to STs related to ST-23 or being part of the ST-23 clonal complex [9]. The lack of β-lactamase in the 3 Hia isolates in this case as well as their uniform sensitivity to the commonly prescribed antibiotics are also common features of Hia in Canada [14], which are in stark contrast to Hib which are more commonly found to have either β-lactamases and/or resistance to antibiotics. Despite susceptibility to antibiotics and aggressive antibiotic treatment, the infant succumbed to the re-infection which may highlight the significance of invasive Hia infections, similar to invasive Hib disease before the introduction of the Hib conjugate vaccine [15]. Another feature in this case noteworthy to mention is the ethnicity of the patient who was described as aboriginal. Related to this point are (a) Hia has recently emerged as a significant invasive pathogen in the aboriginal population in North America in the post-Hib vaccine era [16-18]; (b) in the pre-Hib vaccine era, aboriginal communities in North America have reportedly the highest incidence rates of invasive Hib disease in the world [19-21]; (c) recurrent infections due to Hib [22] and Hia [23] have been reported in the literature. Currently, there are no oro-pharyngeal carriage studies of Hia in aboriginal and non-aboriginal communities in Canada and North America to understand the prevalence of this organism circulating in the population, which probably serves as a source of infection, including the recurrent infection described herein.

Another contributing factor to recurrent Hib (and possibly Hia) infection in young children is the poor immunogenicity of the plain Hib (and likely Hia) capsular polysaccharide and the immature nature of the immune system in young children who do not respond to plain polysaccharide vaccines. The poor immunogenicity of plain polysaccharide vaccines in young children can be overcome by conjugation of the polysaccharide to a carrier protein such as tetanus toxoid. Additional contributing factors may involve potential genetic polymorphism in the antibody encoding genes or genetic loci that may affect antibody acquisition and Hib (possibly Hia) disease susceptibility [24,25]. However, these claims have not been substantiated by further systematic studies.

Besides meningitis [26], Hia has been reported to cause sepsis with toxic shock [27], septic arthritis [28], soft tissue infection with pus and abscess [29], pneumonia with empyema [30], and epiglottitis [31]. Most invasive Hia cases occur in children between the ages of 6 months to 2 years [32; authors' unpublished data]. Case fatality rates have been reported from as low as 2 to 5% [32-34] to as high as 16 to 23% [35,36] and even 33% with infection due to strains possessing the *IS*1016-*bexA* deletion [37]. This vast range of case fatality rates may be related to the patient population as well as to the strains of Hia involved. Previous studies have shown that strains that belong to ST-4 and contain the *IS*1016-*bexA* partial deletion are associated with higher case fatality rates [37,38]. However, in this case, the isolates involved did not possess this genetic deletion and belonged to ST-23. Nevertheless, the infant succumbed to the infection, which may suggest that this common clone of Hia in Canada is still virulent and has the potential to cause fatal infection, similar to the clinical diseases caused by Hib. The spectrum of invasive diseases, their mortality rates as well as ages of the affected subjects are all very similar to the picture associated with Hib in the pre-Hib vaccine era.

Conclusions

The similarities in the microbiology of Hia and Hib as well as the diseases caused by them may suggest that prevention strategies employed for control of invasive Hib disease may be applicable for control of Hia. For example, it is known that close contacts of those with invasive Hib infection are at an increased risk of contracting Hib infection, when compared to the general public, and chemoprophylaxis is recommended for prevention of secondary Hib cases [3,39]. Whether or not chemoprophylaxis offered to household as well as other close contacts of this case would prevent the reinfection in this child cannot be known for sure but should be considered for future studies. The capsule polysaccharide of Hib is a known protective antigen and conjugate vaccine prepared from this antigen has been successfully used to control invasive Hib disease. Conjugated vaccine prepared with the Hia capsular polysaccharide has been proposed as a potential vaccine candidate for prevention of Hia infection [40]. A public health driven vaccine initiative has been established within the Canadian federal government to examine the potential of developing a conjugated Hia vaccine for protection against invasive Hia disease in the Aboriginal population [18,41].

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	KW	PNL	GBH	KC	KH	MS	RSWT
Research concept and design	--	✓	✓	✓	--	--	✓
Collection and/or assembly of data	✓	✓	--	✓	✓	✓	--
Data analysis and interpretation	✓	✓	--	✓	--	✓	✓
Writing the article	✓	✓	--	✓	--	--	✓
Critical revision of the article	✓	✓	✓	✓	--	--	✓
Final approval of article	✓	✓	✓	✓	✓	✓	✓
Statistical analysis	--	--	--	--	--	--	--

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