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Case Report

Pediatric invasive disease due to *Haemophilus influenzae* serogroup A in Riyadh, Saudi Arabia: case series

Zailaie Roaa[1]*, Alawfi Abdulsalam[1]*, Ghazi Shahid[2], Baba Kamaldeen[3], Al Fawaz Tariq[1]

[1] Department of Pediatric Infectious Diseases, Department of General Pediatrics and Microbiology Division, King Fahad Medical City, Riyadh, Saudi Arabia
[2] Microbiology section, Department of Pathology and Clinical Laboratory Medicine, King Fahad Medical City, Riyadh, Saudi Arabia
[3] Department of Medical Microbiology, Faculty of Health Sciences/National Health Laboratory Service, Universitas Academic Laboratory, University of the Free State, Bloemfontein 9300, South Africa

* Both authors contributed equally and shared first authorship.

Abstract

We describe the first two cases of invasive disease caused by *Haemophilus influenzae* serotype A in Saudi Arabia. This is the first known reported invasive *Haemophilus influenzae* serotype A from Saudi Arabia.

Case presentation: A ten-month-old and three-month-old male not known to have any past history of any medical illness and who had received *H. influenzae* type b (Hib) vaccine presented to our hospital mainly with fever of few days' duration. A provisional diagnosis of meningitis with sepsis was made and laboratory tests were requested. The chest radiograph was normal.

The laboratory results revealed leukocytosis, but leukopenia was noticed in the younger infant. Blood culture and cerebrospinal fluid specimens yielded a pure culture of *Haemophilus influenzae* and serotyping showed the isolates to be serogroup A.

Both patients were started on vancomycin and third-generation cephalosporin. On receiving the blood culture result, vancomycin was stopped. Fever subsided after 48 hours, while in the second case, it continued for 12 days from the admission date. The repeat blood cultures were negative. Antibiotic therapy was given for 10 days for the first case with an unremarkable hospital course, while the second case was complicated by seizure and received a longer duration of antibiotics. Both infants were discharged home in good condition.

Conclusions: Invasive non-typeable *H. influenzae* strains are emerging and there is a need for surveillance of this disease. This has implications in future vaccine development.

Key words: *H. influenzae*; meningitis; pediatrics; *H. influenzae* type A.

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Introduction

Haemophilus influenzae is a small, non-motile, non-spore-forming, pleomorphic, Gram-negative coccobacillus; some strains possess a polysaccharide capsule. These strains are serotyped into six different types (A-F) based on the biochemical composition of their capsules. Some strains have no capsule and are termed non-encapsulated or non-typeable *H. influenzae* (NTHi). The different serotypes can be identified with slide agglutination or polymerase chain reaction (PCR) [1].

The most virulent strain is *H. influenzae* type b (Hib), with its polyribosylribitol phosphate capsule. It accounts for more than 80% of *H. influenzae* invasive diseases in children [2]. The other encapsulated strains of *H influenzae* occasionally cause invasive disease similar to that of Hib. To a lesser extent, *H. influenzae* type a (Hia) has been reported to cause invasive disease (*e.g.*, meningitis) clinically indistinguishable from that caused by Hib [3].

We report the first two cases of meningitis due to *H. influenza* serogroup A in infants in Riyadh, Saudi Arabia.

Case 1

H. influenzae serogroup A was isolated from blood culture and cerebrospinal fluid (CSF) samples from a 10-month-old boy admitted to King Fahad Medical City, Riyadh, Saudi Arabia on 18 April 2014 with fever and vomiting of two days' duration. The patient was not known to have any past history of any medical illness and had received two doses of Hib vaccine (information

from parents and the vaccination card). The Hib vaccines were administered at two and four months in accordance with the Expanded Program of Immunization (EPI) schedule of the Kingdom of Saudi Arabia. The third dose of six months was not administered owing to some social problems encountered by the parents.

Examination revealed an ill-looking, lethargic, febrile child (body temperature 39°C, pulse rate 168, respiratory rate 60, blood pressure 101/57mmHg) with a bulging anterior fontanelle. Muscle tone, power, and reflexes were normal. All other systems were normal. A provisional diagnosis of meningitis with sepsis was made and blood specimens for full blood count (FBC), electrolytes, liver function, blood gases, coagulation profile, and blood culture together with cerebrospinal fluid and nasopharyngeal aspirate for respiratory viruses were submitted for analyses. The chest radiograph was normal.

The FBC profile revealed leukocytosis (31.4×10^9/L; normal: $6–18\times10^9$/L); the serum sodium was low (131 mmol/L; normal: 135–145mol/L), but all the other parameters were within the normal range. The CSF white cell count was high (1,215/mm^3 with 86% neutrophils), red cell count was 36/mm^3, the protein value was also high 1.1g/L (normal: 0.15–0.45 g/L), the glucose was low (2.9 mmol/L; serum glucose 5.9 mmol/L), and no organisms were seen on direct Gram stain. The CSF PCR for herpes simplex virus types 1 & 2 was negative. The PCR for respiratory viruses' panel (adenovirus, coronavirus, parainfluenza virus 1–4, respiratory syncytial virus [RSV] A&B, influenza A&B, metapneumovirus, enterovirus, human bocavirus) was also negative. Latex agglutination was negative on CSF. Blood culture and CSF specimens yielded a pure growth within 24 hours of incubation. Identification of bacterial species was performed using a Phoenix automated system (Becton Dickinson, San Diego, USA). Susceptibility was performed using Etest (AB Biodisk Solna, Sweden) according to the breakpoints identified by the Clinical Laboratory and Standards Institute (CLSI) breakpoints. Serotyping was performed by direct agglutination using specific rabbit antisera (BD Bioscience, Sparks, USA). *Haemophilus influenzae* was identified and serotyping revealed that it belonged to serogroup A. The isolate was beta-lactamase negative and susceptible to ampicillin (minimum inhibitory concentration [MIC] 0.38 µg/mL; breakpoint 1 µg/mL) and ceftriaxone (MIC 0.5 µg/mL; breakpoint 2 µg/mL).

The patient was admitted to the intensive care unit with a working diagnosis of meningitis with sepsis, and was started on vancomycin and ceftriaxone therapy (cefotriaxone: 100 mg per kg/day; cefotaxime: 200 mg per kg/day; vancomycin: 60 mg per kg/day). On receiving the blood culture result, vancomycin was stopped and the patient was transferred to the ward after 72 hours in a stable condition. The fever subsided after 48 hours from admission and the repeat blood culture after 48 hours was negative. Antibiotic therapy was given for 10 days and the infant was discharged home in a good condition. Immunological work-up, which included immunoglobulin assay and complement function performed during hospitalization, were normal. Hearing and visual assessment performed during the follow-up period one month after discharge was normal. Institutional approval from King Fahad Medical City Institution review board (IRB00008644) was obtained.

Case 2

H. influenzae serogroup A was isolated from blood culture and cerebrospinal fluid samples from a three-month-old boy who presented at King Fahad Medical City, Saudi Arabia in September 2014. The patient had received one dose of Hib vaccine (information from parents and the vaccination card). The Hib vaccines were administered at two months of age in accordance with the EPI schedule of the Kingdom of Saudi Arabia.

The infant presented to the emergency room with fever and irritability of five days' duration. Examination revealed an ill-looking, lethargic, febrile child (body temperature 39°C, pulse rate 210, respiratory rate 44, blood pressure 90/50mmHg) with a bulging anterior fontanelle. Muscle tone, power, and reflexes were normal. All other systems were normal except for the cardiovascular exam, which revealed a systolic murmur clinically. A ventricular septal defect was detected by echocardiogram; however, there was no vegetation. A provisional diagnosis of meningitis with sepsis was made and blood specimens for FBC, electrolytes, liver function, coagulation profile, and blood culture together with cerebrospinal fluid and nasopharyngeal aspirate for respiratory viruses were submitted for analyses.

The FBC profile revealed leukopenia (2.89×10^9/L; normal: $6–18\times10^9$/L); electrolytes were within the normal range. The CSF white cell count was high (1,224/mm^3 with 89% neutrophils), red cell count was 8/mm^3, the protein value was also high (1.3 g/L; normal: 0.15–0.45 g/L), the glucose was low (2.5 mmol/L; serum glucose 6 mmol/L), and no organisms were seen on the Gram stain. PCR for respiratory viruses' panel (adenovirus, coronavirus, parainfluenza

virus 1–4, RSV A&B, influenza A&B, metapneumovirus, enterovirus, human bocavirus) was also negative. Direct latex agglutination on CSF was negative. Blood culture and CSF specimens yielded a pure growth within 24 hours of incubation. Identification of bacterial species was performed using a Phoenix automated system (Becton Dickinson, San Diego, USA). Susceptibility was performed using Etest (AB Biodisk, Solna, Sweden) according to the breakpoints identified by the CLSI. Serotyping was performed by direct agglutination using specific rabbit antisera (BD Bioscience, Sparks, USA). *Haemophilus influenzae* was identified and serotyping revealed that it belonged to serogroup A. The isolate was beta-lactamase negative and susceptible to ampicillin (MIC 0.5 µg/mL; breakpoint 1 µg/mL) and ceftriaxone (MIC 0.19 µg/mL; breakpoint 2 µg/mL).

The patient was admitted to the pediatric ward with a working diagnosis of meningitis with sepsis and was started on vancomycin and cefotaxime therapy. On receiving the blood culture result, vancomycin was discontinued. The repeat blood and CSF cultures after 72 hours were negative. The fever continued for a total of 12 days. The infant developed four attacks of generalized prolonged seizure, which lasted up to 30 minutes, with left-sided focality on two occasions. A CT scan of the head was done twice and revealed a normal result. Electroencephalography was also done with normal findings. Repeat blood workup revealed leukocytosis and thrombocytosis, improving over time, and a negative culture result as well. Antibiotic therapy was given for 14 days. The patient was discharged home in good condition on phenobarbitone. Hearing and visual assessment performed during the follow-up period one month after discharge was normal.

Discussion

Prior to the introduction of the Hib conjugate vaccine, Hib was the commonest cause of bacterial meningitis in children under five years of age.

Table 1. Studies in the post-Hib vaccination era (N = 15).

Reference	Description	Significant findings
Adderson *et al.* (2001) [7]	Severe Hia invasive disease from Utah, USA	Meningitis and bacteremia in 4 (3 females ages 6, 7, 12 months & 1 male 13 months), and a fifth case of pneumonia.
Ribeiro *et al.* (2003) [8]	Eightfold increase in Hia meningitis in Brazil after introduction of Hib vaccine	Mortality of Hia meningitis (n = 13) was similar to those of non-type A cases including Hib. Isolates from CSF.
Hammitt *et al.* (2005) [9]	Outbreak of invasive Hia disease among Alaska natives	Female (6 months) with Hia meningitis. 2 other cases of arthritis and pneumonia. Hia isolates from CSF, blood and joint fluid.
Kapogiannis *et al.* (2005) [10]	Invasive Hia disease (USA)	Male (30 months) with meningitis and septic arthritis. Isolate from blood, CSF, and synovial fluid. Other case of arthritis.
Millar *et al.* (2005) [11]	Hia from among Navajo and White Mountain Apache children, USA	76 cases of invasive Hia disease with commonest presentation being meningitis, followed by pneumonia; others were cellulitis and septic arthritis.
Tsang *et al*. (2006) [12]	Hia from Manitoba, Canada	20 isolates from children < 24 months and the isolates were from blood and CSF. Other 6 isolates were from adults.
Sill *et al.* (2007) [13]	Hia from Quebec, Canada	4 isolates, 3 from blood culture (2-year-old female, 1-year-old male, and 57-year-old female) and one from ear (10-month-old male).
Bruce *et al.* (2008) [14]	Hia from North American Arctic	38 Hia cases; 30 occurred in children 2–5 years of age and 8 in adults. Clinical presentations were meningitis and pneumonia, followed by septic arthritis.
dePádua *et al.* (2009) [15]	Hia meningitis from Brazil	Female (5 months), CSF culture positive.
Ladheni *et al.* (2010) [16]	Hia from Europe, 1996–2006	26 cases; 17 were < 5 years of age; 4 were 5–64 years; 5 were > 65 years. Meningitis in 23 cases.
Kelly *et al.* (2010) [17]	Hia from Northwestern Ontario, Canada, in 2004–2008.	6 cases presented with respiratory symptoms and one presumed osteomyelitis or septic arthritis of ankle. Hia isolated from blood in all 7 cases; 5 cases in children< 5 years of age and 2 in adults.
Hammitt *et al.* (2006) [18]	Hia from Alaska, USA	6-month-old infant with pneumonia. Isolate from blood culture.
Beazuhly and Fish (2012) [19]	Hia from Halifax, Canada	13-month-old female. Isolate from blood and wound.
Sadeghi-Avala *et al.* (2013) [20]	Hia from Northern Ontario, Canada	18-month-old male; 8-month-old female with meningitis. Two other cases of pneumonia. Isolates from blood and CSF.
Francis *et al.* (2011) [21]	Hia from Western Australia	10-month-old male with septic shock. Isolate from blood.

Hia: Hib: CSF: cerebrospinal fluid.

However, the incidence of invasive Hib disease in children has now decreased dramatically by nearly 99% [4,5]. A recent study from the USA reported *H. influenzae* serogroup A causing invasive disease in 22 of 91 cases of *H influenzae* infections [2]. Approximately half of these were meningitis cases.

A local Saudi Arabian study on the characterization of *H. influenzae* isolates reported only five isolates of serogroup A from children, and all of these were from mucosal sites (non-invasive disease) [6]. We report the first two cases of invasive disease with *H. influenzae* serogroup A causing meningitis in Saudi Arabia.

The infants presented with classical symptoms of sepsis, and the organism was isolated from blood culture as well as CSF samples. The patients had received Hib conjugate vaccine and were not immunocompromised. We could not identify any risk factors for invasive disease by serogroup A. Furthermore, there was no epidemiological link between the two cases as there was a four-month period between presentation and no contact between the two patients. The course of the disease was unremarkable for the first case; the infant received 10 days of intravenous ceftriaxone and was discharged home with full recovery. On the other hand, the course of the disease was complicated by seizure disorder for the second case; the infant received 14 days of intravenous cefotaxime and was discharged home with anti-epileptic medications. Follow-up visits to assess hearing and vision impairment were negative and the seizure was well controlled, indicating excellent recovery without any long-term adverse sequelae.

H. influenzae serogroup A infections have been reported from other countries, mainly from North America, as shown in Table 1.

Although Hia has the potential to cause outbreaks, only one outbreak has been reported in the literature [9]. Very few studies have examined Hia carriage rates, but in two studies performed in Alaska, rates of 16%–43% were found among close contacts of a culture-confirmed Hia invasive disease case patient [9,18]. The Alaskan population may lend itself to heavier colonization rates. We did not examine the carrier state in our patients and their contacts nor did we provide any prophylaxis.

Judging by the number of cases of Hia occurring in vaccinated populations as well as in our patients who had received two doses of Hib, there appears to be no cross-protection. This raises the prospect of development of Hia conjugate vaccines; however, more research is needed towards a better understanding of epidemiology of invasive Hia disease.

Conclusions

Continuing surveillance is essential for all *H. influenzae* infections, especially in the post-Hib vaccination era, as non-b serotypes and non-typeable *H. influenzae* strains may become major cause of invasive diseases.

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Authors' contributions

ZR and AA manage patients, collected data, wrote paper and review paper; GS and AT supervise management and review paper; KB wrote and review paper.

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Corresponding author

Baba Kamaldeen
Department of Medical Microbiology
Faculty of Health Sciences/National Health Laboratory Service
Universitas Academic Laboratory
University of the Free State
Bloemfontein 9300, South Africa
Phone+27 514052981
Fax+27 514443437
Email: adeola12@yahoo.co.uk

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