CASE REPORT

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Report of *Haemophilus Influenzae* serotype a intracranial infections in older children

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ABSTRACT

Introduction: *Haemophilus influenzae* (Hi) is subdivided into typeable (a–f) and non-typeable groups. Hi serotype b (Hib) has historically been one of the important pathogens responsible for invasive infection. However, after widespread Hib vaccination, the emergence of other Hi serotypes, specifically Hi serotype a (Hia), was noted during the last few decades, mostly in children younger than 5 years of age.

Case presentation: We present two cases of severe intracranial infections with detected Hia in patients > 5 years of age within a short time frame and within the same geographic area.

Conclusion: Epidemiological studies and surveillance on Hia-related illnesses in all age groups worldwide are needed to better understand the clinical and epidemiological characteristics of Hia. This can establish a platform to develop a candidate vaccine against Hia that might protect children of all ages.

KEYWORDS
Haemophilus influenzae serotype b, intracranial infection, vaccine, epidemiology

INTRODUCTION

Haemophilus influenzae (Hi) is a pleomorphic Gram-negative coccobacillus known to colonize nasopharyngeal mucosal membranes in young children, an important risk factor for invasive infection.[1,2] Hi is subdivided into two main groups: capsulated (typeable) with 6 different serotypes (a–f) identified by the antigenic makeup of their polysaccharide capsules that determine pathogenicity and invasiveness, and the non-capsulated (non-typeable) group.[3] Before the Hi serotype b (Hib) vaccine era, the non-capsulated Hi was considered to be a colonizer rather than a true pathogen.[4]

Historically, Hib was the leading cause of a variety of illnesses including otitis media, meningitis, epiglottitis, pneumonia, sepsis, arthritis, and cellulitis in children and adults in the pre-vaccine era, with high mortality and morbidity rates.[5,6] Hib was also a major cause of pyogenic meningitis in young children < 5 years of age worldwide until the introduction of the Hib vaccine in 1987.[5,7] Since then, there has been a drastic decline in the annual incidence

and rate of Hib infections. The marked reduction in Hib morbidity and mortality in children < 5 years of age likely occurred through intensification of herd immunity against Hib,[8,9] and a switch in circulation to non-Hib serotypes (Hi types a, c, d, e, and f) and non-typeable Hi. This led to an increase in illness burden from non-Hib serotypes and non-typeable Hi, thus filling the ecologic niche previously occupied by Hib.[10,11]

Ongoing surveillance studies in the United States (U.S.) report the incidence and rates of Hi infections (Hib, non-Hib serotypes, and non-typeable Hi) in children < 5 years.[12–15] However, the data does not provide a clear understanding of the epidemiology of Hi serotype a (Hia) in children > 5 years of age. We report 2 cases of invasive Hia in older children presenting to our hospital during December 2021–January 2022.

CASE REPORT

Patient A

Patient A is a seven-year-old male with sickle cell β-Thalassemia and functional asplenia, never required any blood transfusions, and was fully vaccinated. He was admitted from an outside hospital with lethargy, intermittent fevers (maximum temperature of 39.9 °C), worsening frontal headaches and nasal congestion for 3 weeks, and progressively worsening periorbital edema for 2 days. In the outside hospital computed tomography (CT) scan of the head demonstrated bilateral frontal extra-axial fluid collection concerning abscess, with brain compression and localized mass effect. Patient was given ceftriaxone and transferred to our hospital. On admission, his temporal temperature was 37.1 °C, heart rate (HR) was 126/min, respiratory rate (RR) was 26/min, blood pressure (BP) was 102/56 mmHg, and oxygen saturation was 100%. A complete blood count (CBC) on admission showed a normal white blood cell count (WBC) and microcytic anemia. The patient was started on levetiracetam for seizure prophylaxis. Magnetic resonance imaging (MRI) of the brain with and without intravenous contrast, and magnetic resonance venography with contrast showed frontal, maxillary, and ethmoid sinusitis complicated by two large lenticular collections over the anterior frontal convexities (measuring 7.1 cm × 4.8 cm × 2.8 cm to the left of the midline and 4.2 cm × 1.7 cm × 2.3 cm on the right). There were also several small abscesses of the frontal bones measuring up to 1.0 cm × 0.5 cm × 1.4 cm indicating osteomyelitis with local mass effect on the frontal lobes, but with no significant midline shift. Distortion of the anterior superior sagittal sinus by local mass effect with areas of nonenhancement concerning focal thrombosis was also reported. The patient was taken to the operating room and underwent bifrontal craniotomy with evacuation of the epidural abscess, insertion of Jackson-Pratt drain, and bilateral endoscopic sinus washout. The patient continued on ceftriaxone (50 mg/kg

every 12 hours), and vancomycin (20 mg/kg every 6 hours) with metronidazole (7.5 mg/kg every 6 hours) was added to the treatment regimen. The Gram stain of fluid drained from his brain abscess showed Gram-positive cocci in chains that were identified as pan-susceptible *Streptococcus intermedius*. Washout of the left maxillary sinus culture grew β-lactamase positive Hi, subsequently identified as Hia by the local health department. The patient had an uncomplicated hospital stay and was discharged home to complete 6 weeks of ceftriaxone monotherapy. He was followed in the outpatient pediatric infectious diseases clinic and completed his planned treatment regimen without any complications.

Patient B

Patient B is a six-year-old previously healthy and fully immunized male who presented to our hospital with a fever (up to 39.4 °C) associated with shivering, headache, one episode of emesis, sudden hearing loss, confusion, brief episodes of visual hallucinations and progressive worsening of neck stiffness during the 24 hours prior to admission. The history was remarkable for hitting his head and having his right eye punched while on the school bus several hours before symptom onset. Upon arrival at our emergency department, the patient's temporal temperature was 36.2 °C, HR was 98/min, RR was 19/min, BP was 93/56 mmHg, oxygen saturation was 100%. His physical examination was remarkable for forehead swelling and ecchymosis, confusion, hearing loss, and nuchal rigidity. The patient underwent a lumbar puncture with opening pressure 46 cmH$_2$O (reference range 6–25 cmH$_2$O). Cerebrospinal fluid (CSF) showed 1.825×10^9/L WBC (reference range $<0.010 \times 10^9$/L), differential: 95% neutrophils, 5% monocytes, 0.385×10^9/L red blood cells (reference range $< 0.001 \times 10^9$/L), hypoglycorrhachia with glucose < 1 mg/L (reference range 4.5–7.5 mg/L), protein 32.1 mg/L (reference range 1.2–6.0 mg/L), and Gram-negative bacilli on CSF Gram stain. CBC was unremarkable. Head CT scan showed prominence of the bifrontal extra-axial spaces (left slightly greater than right) suspicious for subdural collections, ethmoid and sphenoid sinus mucosal thickening with partial opacification, and incidental findings for anatomical abnormality of the skull base. Brain MRI with and without contrast confirmed findings of small subdural empyema in the left frontal subdural space, cerebritis in the left frontal lobe, meningeal enhancement, and mild ethmoid and left sphenoid mucosal thickening. The patient was started on empirical treatment with cefepime (50 mg/kg every 8 hours), and vancomycin (20 mg/kg every 6 hours). Within the next 24 hours, the blood cultures grew β-lactamase negative Hi, subsequently identified as Hia by the local health department.

The patient underwent left frontal craniotomy for partial resection of phlegmon with the placement of left

frontal external ventricular drain (EVD) and left frontal intraparenchymal intracranial pressure monitor. Cefepime and vancomycin were de-escalated to monotherapy with ceftriaxone (50 mg/kg every 12 hours) for Hia coverage.

After EVD removal on hospital day 11, the patient developed re-accumulation of fluid over the left frontal craniotomy site and EVD site leakage associated with headache and emesis necessitating EVD replacement, and subsequent ventriculoperitoneal shunt insertion due to persistently elevated intracranial pressure. The rest of the hospital course remained unremarkable. The patient was discharged after he completed a total of 4 weeks of antibiotic therapy.

The patient was also diagnosed with profound bilateral hearing loss as a complication and underwent a cochlear transplant on both sides three months after his hospital discharge. Immunologic work-up resulted in normal T and B lymphocyte subset panel and normal serum immunoglobulin levels. However, he had an inadequate post-13-valent pneumococcal conjugate vaccine (PCV13) response to < 40% of pneumococcal vaccine serotypes and low diphtheria antibody titers despite receiving routine vaccinations and boosters recommended in the U.S.[16] The total complement (CH-50) level was normal. The patient received the 23-valent pneumococcal polysaccharide vaccine (PPSV23) before discharge and responded well with appropriate seroconversion.

DISCUSSION

There are growing numbers of sporadic case reports, case series, and retrospective studies with various clinical presentations of invasive Hia infection globally.[17–31] Most of these reports show the greatest burden of invasive Hia disease in children ≤ 5 years or adults > 65 years,[32] with short- and long-term adverse outcomes exclusively in young children ≤ 5 years of age.[23,31,33]

We described two cases of invasive Hia infection in children > 5 years of age who presented within a 2-month period to our hospital. There was no identifiable epidemiological link between these patients and both cases were unrelated. While both had severe diseases, patient B had an extremely complicated clinical course with permanent hearing loss, while patient A recovered without any major sequelae. Although both presented with fever and neurological symptoms and were diagnosed with meningitis, the risk factors and pathophysiology of both cases seem to be different. In patient A, it is possible that Hia isolated from the left maxillary sinus played a synergistic role in pathogenicity, along with *S. intermedius* which was isolated from both sinuses and brain abscess. This patient had a good response to management with both surgery and antimicrobial therapy, despite his underlying functional asplenia from sickle cell β-Thalassemia. Patient B, on the other hand, had an

abrupt onset of symptoms after facial trauma and developed severe invasive Hia infection despite being previously healthy. He had a complicated course requiring multiple neurosurgical interventions and had profound hearing loss as a long-term complication. His baseline immunologic evaluation was normal except for low pneumococcal titers after receiving the PCV13 series.

The severity of Hia infection in children > 5 years can be explained by the acquisition of virulence factors through horizontal transfer of DNA deletion from certain Hib clones,[34] or mutation in the genome of existing circulating Hia[35] leading to the emergence of highly pathogenic Hia.

Given the novelty of our cases such as the presentation of intracranial infections with detected Hia in both patients > 5 years of age within a short time frame and within the same geographic area, we were tempted to hypothesize that a highly pathogenic variant of Hia was circulating in the community. This hypothesis could be supported by previously reported observation during the investigation of the Hia outbreak in Alaska in 2003 when Hia carriage was identified in contact with patients with invasive Hia, confirming the circulation of pathogenic strains.[36] However, it is likely that isolates from our cases belong to different Hia clones given that one isolate was β-lactamase positive and the other β-lactamase negative, yet we cannot state this with certainty since we were unable to perform whole genome sequencing for identification of clonal relatedness.

In population-based surveillance studies worldwide and in the U.S., most of the reports of invasive Hi infections are restricted to Hib, non-Hib, and unknown serotype Hi infections.[37] Few U.S. surveillance studies include data on Hia which demonstrate the increase in the incidence of invasive Hia illnesses in children < 5 years old.[14,33] Specifically, the latest study from the Active Bacterial Core surveillance (ABCs) showed that the incidence of Hia infection during the 2002–2008 period increased by 148% in all ages, with an estimated 13% annual increase in incidence during the 2002–2015 period.[14] The burden of all Hi serotypes was minimal in patients 5–17 years old, whereas the highest incidence of invasive Hia was observed in young American Indian and Alaska Native children < 1 year of age (16.94 per 100 000).[14] It is noteworthy that the ABCs study captured only 10 states, so generalizability might be not realistic with an underestimation of the actual epidemiology of Hia invasive infection that varies geographically. This was described in a very recent report by the same ABCs research group that demonstrated the difference in the incidence of Hia infection in Alaska compared to the U.S. overall incidence.[38]

Outside the U.S., the most recent reported surveillance on Hi from 2018 conducted in 30 countries by the European Center for Disease Prevention and Control (ECDC) showed

that non-capsulated Hi strains were responsible for 78% of invasive infection in all age groups, with other Hi serotypes contributing to the rest of the cases. This includes 9% Hi serotype f, 7% Hib, 3% Hi serotype e, and 2% non-Hib (Hia, serotypes c and d).[39]

Early notification of Hi invasive infection in children is required in the U.S. Each state has different regulations and requirements regarding the age and specific Hi serotypes reporting.[13] Some state labs are required to report Hi infection in children < 5 years, others for all age groups. The Centers for Disease Control and Prevention annual ABCs report includes Hib, non-Hib, non-typeable, and unknown Hi in all age groups.[40] Whereas the ECDC report includes data from comprehensive passive surveillance systems with national coverage, sentinel surveillance systems, or aggregated data on invasive Hi infection in all age groups from 30 European Union or European Economic Area Member States with serotyping data available only in 57% of confirmed cases.[39] Multiple reports on Hia invasive infections worldwide highlight the necessity for more surveillance and local epidemiological studies on Hia-related illnesses. Furthermore, ongoing concerns about the emergence of invasive severe Hia and high susceptibility of vulnerable population groups (anatomical or functional asplenia, congenital or acquired immunodeficiency, medically complex patients) to Hia infection, as well as the lack of cross-reactivity between Hib and Hia strains emphasizes the need for the development of Hia vaccine.[41,42]

In summary, we presented two cases of intracranial infections with detected Hia in patients > 5 years of age within a short time frame and within the same geographic area. Scrupulous monitoring of Hia infection in all pediatric age groups worldwide will allow a better understanding of the clinical and epidemiological characteristics of Hia. This can establish a platform to develop a candidate vaccine against Hia that might protect children of all ages.

CONSENT FOR PUBLICATION

Consent was obtained from the patient's guardian.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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