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Case Report: Invasive Non Type b *Haemophilus influenzae* in Immunocompromised Children

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection GBCDEF **Giselle Gayle Gozum**
CDEF **Oksana Tatarina-Nulman**
ABCDE **Minnie John**Department of Pediatrics, New York-Presbyterian Brooklyn Methodist Hospital,
Brooklyn, NY, U.S.A.**Corresponding Author:** Oksana Tatarina-Nulman, e-mail: okt7001@nyp.org**Conflict of interest:** None declared**Case series****Patients:** Male, 2-year-old • Male, 4-year-old • Male, 2-year-old**Final Diagnosis:** Immunodeficiency and Hib**Symptoms:** Fever • lethargy • reduced food intake**Medication:** —**Clinical Procedure:** —**Specialty:** Immunology**Objective:** Unusual clinical course**Background:** Implementation of the *Haemophilus influenzae* type b (Hib) conjugate vaccine brought about a reduction in the number of cases and morbidity from type B but increase in nontypeable strain infections.**Case Reports:** We had 3 cases of invasive non type *Hemophilus influenzae* (NTBHI) in immunocompromised children. The first was a fully vaccinated 2-year-old male with a history of pseudomonas sepsis who presented with 1 day of lethargy, fever, vomiting, and diarrhea. Blood culture was positive for *Haemophilus influenzae* e and cerebrospinal fluid (CSF) confirmed meningitis. Immune deficiency and genetic testing revealed X-linked agammaglobulinemia. The second case was a 4-year-old male, status post liver transplantation, who presented with pneumonia, with positive blood culture for *H. influenzae*. The last case was of a 2-year-old male with *H. influenzae* b-type VI in both blood and CSF cultures, who on follow-up was confirmed to have hypogammaglobulinemia.**Conclusions:** For children diagnosed with an invasive disease caused by NTBHI, a workup for immunodeficiency could be warranted. With the appearance of nontype b serotypes, more studies are needed to determine epidemiology and virulence of these types, and their clinical relevance – perhaps developing a new vaccine to cover nontype b stereotypes, especially for immunodeficient patients.**MeSH Keywords:** **Haemophilus Infections • Haemophilus influenza • Haemophilus influenzae type b • Immunocompromised Host • Pediatrics****Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/920853>

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Background

Haemophilus influenzae is a Gram-negative, pleomorphic coccobacillus that requires factor X (hematin) and factor V (phosphopyridine nucleotide) for growth. Some *H. influenzae* isolates have a polysaccharide capsule and can be serotyped into 6 antigenically and biochemically distinct types designated a, b, c, d, e, and f. Most isolates are nontypeable. Humans are the only natural hosts for the bacteria [1].

Haemophilus influenzae causes invasive diseases such as bacteremia and meningitis. *H. influenzae* b (Hib) is commonly responsible for such infections. Implementation of the Hib conjugate vaccine brought about a reduction in the number of cases and morbidity from type b [2]. However, the vaccine does not offer protection from nontypeable strains, thus causing an epidemiologic shift to nontypeable strain infections. The Centers for Disease Control and Prevention (CDC) 2016 Active Bacterial Core Surveillance (ABCs) data reported 1.99 cases in 100 000 population and 0.29 deaths in 100 000 population for invasive disease. Prior to the vaccine, there were 64 to 129 cases per 100 000 children with invasive disease who were younger than 5 years old. *H. influenzae* morbidity statistics identified 54 cases of meningitis with 3 deaths, 199 cases of bacteremia without a focus with 23 deaths, and 497 cases of pneumonia with bacteremia with 74 deaths. The CDC noted that most infections caused by *H. influenzae* were from nontypeable strains, with 192 cases of other serotypes, including type e [3]. With the decline of diseases caused by type b organisms, diseases caused by other serotypes and nontypeable organisms has become more recognized [3,4]. Limited studies have been published regarding other serotypes of *Haemophilus influenzae*.

Case Reports

We present 3 cases of invasive NTBHI infections in children with immunodeficiency, who presented within the past year to our institute. These cases were reviewed and acknowledged by the Institutional Review Board.

Case 1

Patient A was a 2-year-old male, fully immunized, with a history of recurrent fever and ear infections requiring bilateral tympanostomy tube placement since 7 months of age. He was admitted to the Pediatric Intensive Care Unit (PICU) for pseudomonas sepsis at 15 months of age. The patient presented to the emergency department (ED) with a 1-day history of lethargy, fever, non-bilious, non-bloody vomiting, and non-bloody, non-mucoid diarrhea. He was febrile, irritable, but consolable. His physical examination was normal except for dehydration. The patient was moving all extremities equally;

he had no stiffness, and he had normal reflexes in all extremities. His cranial nerves II-XII were grossly intact.

Laboratory investigation showed marked leukocytosis to 41 000/uL (normal range: 5000–15 000/uL), neutrophil predominant with 38% bands. C-reactive protein (CRP) was elevated to 254 mg/L (normal <2.9 mg/dL) and platelets were elevated to 545 000/uL (normal range: 117 000–361 000/uL). The patient's basic metabolic profile was unremarkable. His chest radiograph was normal. An influenza polymerase chain reaction (PCR) assay was negative. The urinalysis was unremarkable, and the urine culture had no growth.

The patient was admitted to the PICU and was initially treated with piperacillin-tazobactam and vancomycin. His blood culture was positive for Gram-negative rods. Upon receipt of the positive blood culture results, we performed a lumbar puncture, and the blood culture was repeated. His cerebrospinal fluid (CSF) showed glucose at 38 mg/dL (normal range: 40–70 mg/dL), protein at 53 mg/dL (normal range: 15–45 mg/dL), white blood cell (WBC) count at 2465/uL, red blood cell (RBC) count at 25/uL, 86% neutrophils, 3% lymphocytes, and 21% monocytes. CSF Gram stain showed many WBCs with no organisms. The patient was switched to intravenous ceftriaxone at a meningitic dose of 100 mg/kg/day, and gentamicin. The initial blood culture grew *Haemophilus influenzae* type e. The serotype was confirmed by the New York City Department of Health (NYC DOH) laboratory via the slide agglutination test with commercial antisera (Difco). The repeat blood cultures were negative and the patient clinically improved.

The patient completed 10 days of ceftriaxone at the aforementioned meningitic dose. He was discharged home on day 10 with his activity level at baseline and no neurologic deficits. He was given referrals to genetic and immunology specialists. The patient's workup for immunodeficiency showed X-linked agammaglobulinemia, warranting monthly intravenous immune globulin (IVIG) and sulfamethoxazole/trimeoprim prophylaxis.

Case 2

Patient B was a 4-year-old male, fully immunized, with a history of neonatal hemochromatosis. He was post-liver transplantation at 5 months of age and was currently on maintenance doses of sirolimus 0.6 mg daily. The patient presented with a 2-day history of cough and rhinorrhea, and a 1-day history of fever, chills, and decreased oral intake. At his pediatrician's office, the patient was febrile and tachypneic and was immediately sent to the ED. Upon examination in the ED, he was found to be febrile with a temperature of 38.8°C, tachycardic with a heart rate of 150 beats per minute, tachypneic with a respiratory rate of 30 breaths per minute, and had oxygen saturation

at 96% on room air. Physical examination revealed nasal congestion and decreased breath sounds in bilateral lung bases.

Laboratory examination was remarkable for leukocytosis of 13 000/uL (normal range: 4000–10 3000/uL) with neutrophilia 87.3%. Blood culture was sent for analysis. His chest radiograph showed opacity in the left parahilar region mid-lung zone suggestive of pneumonia.

The patient was admitted to the general pediatric floor. He was empirically treated with ceftriaxone 50 mg/kg daily and continued on his home medication, Rapamune. The blood culture grew beta-lactamase negative *Haemophilus influenzae* at 37 hours of incubation. Another blood culture was drawn, which was negative. The patient was continued on ceftriaxone and received 7 days of intravenous antibiotics. He showed clinical improvement and was discharged home on amoxicillin/clavulanic acid to complete 10 days from the negative blood culture. *H. influenzae* was not typed as the sample was deemed unsuitable.

Case 3

Patient C was a 2-year-old male with a history of acute otitis media and pneumonia 1 month prior to presentation. The patient was on a delayed vaccination schedule but had completed the Hib vaccination series. He presented to the ED with a 1-day history of fever 38.5°C (101.4°F) to 38.9°C (102°F), vomiting, and decreased oral intake and urine output. An hour prior to presentation, he was reported to have had a seizure-like activity lasting for approximately 1 minute. There was no history of head trauma. In the ED, he had a fever of 38°C, and he was tachycardic at 156 beats per minute. He was lethargic, pale, and responded to vocal and pain stimuli. His physical examination showed bilateral tympanic membrane effusion. His neurologic examination was unremarkable. He was given a bolus of normal saline. He had additional episodes of seizure activity noted in the ED.

Laboratory examination was remarkable for WBC 20 000/uL (normal range: 4000–10 3000/uL) with neutrophilic predominance and bandemia of 30%. Metabolic profile and liver function tests were unremarkable. Urinalysis and urine culture were unremarkable. CSF studies showed low glucose of <1 mg/dL (normal range: 40–70 mg/dL), elevated protein of 218 mg/dL (normal range: 15–45 mg/dL), RBC 1050/uL, WBC 2070/uL with 95% neutrophils. Blood culture was positive after 13 hours for *H. influenzae* biotype VI. CSF culture grew the same organism as the blood culture. There was no other organism identified from the culture. A head computed tomography scan was performed, which showed pan sinus opacification.

The patient was admitted to the PICU. He received a 2-week course of ceftriaxone. The results of the video electroencephalogram (EEG) were normal. Immunodeficiency workup was remarkable for a decreased level of all immunoglobulins. Genetic testing revealed X-linked agammaglobulinemia.

Discussion

We present 3 cases of invasive NTBHI in fully immunized patients with immunodeficiency, who presented at our institution within the last year. Another study, by Antony et al., described invasive NTBHI infection in 17 children [5,6]. The Antony et al. study did not note if the children had risk factors for immunodeficiency. There have also been case reports about NTBHI from England and Wales [7] and from the USA [8]. These case reports were of previously healthy children with no risk factors for being immunocompromised. In our case series, the NTBHI infections occurred in immunocompromised patients.

Immunocompromised patients are known to be more susceptible to certain infections, with patients with X-linked agammaglobulinemia and asplenic individuals more predisposed to encapsulated bacteria such as *H. influenzae* and *Streptococcus pneumoniae* [1,9]. The decline of Hib cases after the development of the vaccine raises the question of clinical relevance of nontype b serotypes. With the emergence of nontype b serotypes, importance should be stressed on its burden, especially in the pediatric population [10,11]. Identification of the specific serotype, as well as further research into each serotype, will help determine overall disease burden. In 2 of the 3 cases we report here, immunodeficiency workup followed an invasive infection with NTBHI.

The 6 serotypes of encapsulated *H. influenzae* were described as early as the 1930s; the type b serotype has been found to be more virulent for humans, for unknown reasons. Much has been studied regarding Hib. Before the type b conjugate vaccine was introduced, type b serotype was most likely to be found as a common nasopharyngeal colonizer and a common cause of invasive disease, with type d and type e as the second and third most common [12,13]. Invasive disease caused by other encapsulated serotypes continues to occur, albeit less frequently. There is limited information available on immunity from and epidemiology of nontype b strain infections. It is not clear whether the epidemiologic features of type b disease apply to disease caused by nontype b isolates.

Conclusions

This case report highlights the importance of NTBHI serotypes, especially in immunocompromised patients [12].

More studies are needed to determine the epidemiology and virulence of these types and their clinical relevance. For children diagnosed with an invasive disease caused by NTBHI, a workup for immunodeficiency could be warranted. There is a need for the development of a vaccine for non type b *H. influenzae*, especially for immunodeficient patients.

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Conflict of interest

None.