[CASE REPORT]

Bacterial Meningitis Caused by β-lactamase Non-producing Ampicillin-resistant *Haemophilus influenzae* Type f in an Immunocompetent Woman

Shinya Sakamoto and Naoya Sakamoto

**Abstract:**
We report the case of a 36-year-old previously healthy woman who presented with fever and headache. Blood and cerebrospinal cultures and a bacterial analysis revealed the presence of β-lactamase non-producing ampicillin-resistant *Haemophilus influenzae* type f (Hif) with sequence type 124. Accordingly, the patient was diagnosed with bacterial meningitis with bacteremia caused by Hif. She had normal humoral immunity, and antibiotic therapy rapidly improved her condition. Our case indicates that serotype replacement can occur in Japan and suggests that a certain sequence type causes invasive *Haemophilus influenzae* disease, regardless of host immunity.

**Key words:** *Haemophilus influenzae* type f, invasive *Haemophilus* disease, bacterial meningitis, β-lactamase non-producing ampicillin-resistant *Haemophilus influenzae*

(Intern Med 58: 307-310, 2019)  
(DOI: 10.2169/internalmedicine.0597-17)

**Introduction**

*Haemophilus influenzae* strains are classified as typeable (types a-f) or non-encapsulated. Because *H. influenzae* type b (Hib) causes invasive disease in young children, as well as immunocompromised adults, Western countries developed a Hib vaccine in the 1990s. Other countries subsequently did so, including Japan, which established a publicly subsidized Hib vaccination program in 2011. The incidence of Hib infections has decreased due to Hib vaccination; however, the incidence of non-Hib infections has increased (1, 2). *H. influenzae* type f (Hif) is the most common non-b type, and the incidence of Hif infections has risen in the USA, England, Wales, Canada, and Iceland (2-5).

Five cases of invasive disease due to Hif were recently reported in Japan (6-8), all occurred in immunocompetent young children and adults with underlying conditions. Four of the five cases were considered “typical” (i.e., patients were infected with ampicillin-susceptible Hif). We herein report an atypical case of bacterial meningitis with bacteremia caused by β-lactamase non-producing ampicillin-resistant (BLNAR) Hif in an immunocompetent woman.

**Case Report**

The patient was a 36-year-old woman with no significant medical history. Although she had no apparent sick contacts—including family members—she had a cough, sore throat, and purulent rhinorrhea for approximately two weeks prior to seeking medical attention. The rhinorrhea persisted, whereas the other symptoms improved. She presented to a hospital with fever and headache. At that time computed tomography (CT) of the head showed no abnormalities, and she was discharged. However, her headache worsened, and she was admitted to our hospital the following day.

The patient was unemployed, had reportedly never smoked, and was not pregnant. She lived with her husband and 5-year-old daughter, who had been receiving scheduled Hib vaccinations. A physical examination revealed a body temperature of 37.5°C, a blood pressure of 117/80 mmHg, a heart rate with a sinus rhythm of 75 beats/min, a respiratory rate of 20 breaths/min, and a consciousness level of II-30 on the Japan Coma Scale and E3V5M6 on the Glasgow Coma
the deduced amino acid sequence of the sequence type 124 (ST124) (10). Moreover, we investigated reaction (9). Multilocus sequence typing revealed that it was era (Denka Seiken, Tokyo, Japan) and a polymerase chain

patient with bacterial meningitis with bacteremia caused by

influenzae

H.

and Company, New Jersey, USA), (Table). Using the nitrocefin disc method (Becton Dickinson

and CSF cultures. Intravenous antibiotic therapy (ceftriax-

ation, the presence of

H. influenzae

was confirmed in blood

and ampicillin (12 g per day). Immediately after admission, gram staining of a CSF sample revealed gram-negative bacilli (Figure); thus, dexamethasone, vancomycin, and ampicillin were discontinued. On the 2nd day of hospitalization, the presence of H. influenzae was confirmed in blood and CSF cultures. Intravenous antibiotic therapy (ceftriax-

one) was continued in accordance with the sensitivity results (Table). Using the nitrocefin disc method (Becton Dickinson and Company, New Jersey, USA), H. influenzae isolated from the patient was found to be β-lactamase non-

producing, and was consequently identified as BLNAR H. influenzae. Based on the culture results, we diagnosed the patient with bacterial meningitis with bacteremia caused by H. influenzae. Hif was identified via serotype-specific antisera (Denka Seiken, Tokyo, Japan) and a polymerase chain reaction (9). Multilocus sequence typing revealed that it was sequence type 124 (ST124) (10). Moreover, we investigated the deduced amino acid sequence of the fstI gene encoding penicillin-binding protein 3 in the Hif strain isolated from this patient (11). The Hif strain had an amino acid substitu-

tion (Asn526Lys), which is reported to be one of the most common amino acid substitutions in the fstI gene in BLNAR (11).

**Table.** Minimal Inhibitory Concentrations (MICs) and Antimicrobial Susceptibility Testing of Haemophilus influenzae Type f Isolated from the Patient.

| Antimicrobial agent | MIC (μg/mL) | Interpretation* |
|---------------------|------------|-----------------|
| Amoxicillin         | 4          | R               |
| Amoxicillin-sulbactam | 4         | R               |
| Amoxicillin-clavulanate | 4         | R               |
| Cefaclor            | 8          | R               |
| Cefotaxime          | <0.12      | S               |
| Ceftriaxone         | <0.12      | S               |
| Meropenem           | 0.25       | S               |
| Clarithromycin      | 4          | S               |
| Ciprofloxacin       | <0.12      | S               |
| Trimethoprim-sulfamethoxazole | <0.25 | S |
| Chloramphenicol     | <0.5       | S               |
| Tetracycline        | <0.5       | S               |

*Antimicrobial susceptibility testing was conducted using the microdilution method and judged according to the categories of the Clinical Laboratory Standards Institute.

R: resistant, S: susceptible

The patient’s humoral immunity status was further investigated. Her spleen appeared normal on abdominal ultrasound, and her complement and immunoglobulin levels were within the normal ranges. After 14 days of antibiotic therapy, she was discharged from our hospital with no sequelae.

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

**Discussion**

We encountered a case of bacterial meningitis due to Hif in an immunocompetent woman. She had persistent purulent rhinorrhea for two weeks before the onset of bacterial meningitis, and mucosal thickening in the bilateral maxillary sinus detected by CT was comparable to acute sinusitis. We therefore considered that acute sinusitis could lead to bacterial meningitis.

The H. influenzae strain that causes invasive disease in Japan and other countries with Hib vaccination programs appears to have shifted from Hib to non-b types (1, 2). Due to this shift and consequent changes in clinical features, the number of atypical cases, including those involving immunocompetent patients, will likely increase. ST124 is the most common Hif sequence type in Hif-triggered invasive diseases in some countries (2, 9, 12). In Japan, it was identified in four of the five reported Hif cases (6-8), as well as our own. Accumulating reports on Hif infection suggest that the severity of the infection may be determined by the sequence type, irrespective of the patient’s humoral immunity status. Thus, even in the era of Hib vaccines, physicians should consider Hif and other H. influenzae serotypes, including non-typeable serotypes, when they encounter patients with severe infections, such as bacterial meningitis.

Invasive Haemophilus disease (IHD) is caused by Hib in
affected children; however, the increasing prevalence of Hif may shift the clinical picture from a childhood disease to a senior disease, and IHD may become associated with a higher mortality rate. Originally-as with Hib-Hif has a high inhibitory effect on an alternative pathway (13), which is considered to be likely to cause IHD. However, although the detailed reasons are unknown, many reports have shown that Hif is more common in elderly people and has a higher mortality rate (2, 14, 15). There have been numerous cases of meningitis caused by Hif in children since it was first reported in 1945 (16), with many cases found in immunocompetent children; the mortality rate in such cases is low. On the other hand, to our knowledge, there have only been three reported cases of meningitis due to Hif in adults (17-19), and all cases had underlying disease; one case was deceased. This suggests that elderly people may be at greater risk due to underlying diseases. Hib infection is typically a childhood infection and the incidence dramati
cally decreases with vaccination. Thus, elderly patients require early physician attention as the mortality rate of Hif may be higher in elderly people with underlying diseases.

The antibiotic resistance of non-b types of H. influenzae is a matter of concern. Little information on the antibiotic resistance of Hif exists, with only a few studies in Japan. In the present case, the Hif strain was found to be BLNAR. The number of BLNAR Hib strains had been increasing prior to the introduction of the Hib vaccine (20), and careful monitoring of the number of ampicillin-resistant Hif, including BLNAR strains, is necessary. In the study by Hoshino et al., one of the three Hif strains isolated from Japanese children required higher concentrations of β-lactam antibodies for growth inhibition than the others; hence, this strain had a lower binding affinity for and susceptibility to these antibiotics (7). In a Canadian study (21), although β-lactamase production was reported to show ampicillin toler-
ance, BLNAR was not observed.

Although there have been no reports evaluating the association between the incidence of non-b type H. influenzae infections and living with children vaccinated for Hib, the introduction of the Hib vaccine in the community may be a predisposing factor for the increasing number of non-type b H. influenzae infections. In a study in Italy, the H. influenzae strains isolated from the oropharynges of young (<6 years of age) Hib-vaccinated children were predominantly non-typeable H. influenzae (11); however, there is no evidence of Hif colonization after Hib vaccination. Because naso-
apharyngeal colonization changes may occur in children with a complete Hib vaccination status, the adults residing with them may be susceptible to non-b types, such as Hif. Thus, physicians should consider the vaccination history of the patients’ family members when treating patients with severe infections. This information may help physicians identify the responsible pathogen and select the most effective antibiotic therapy.

The number of atypical presentations of invasive H. influ-
enzae disease, including diseases involving immunocompe-
tent hosts, may be increasing in the Hib vaccination era due to a serotype shift from Hib to non-type b strains. Hence, physicians in Japan should pay careful attention to the surve-

The authors state that they have no Conflict of Interest (COI).

Acknowledgments
The authors thank Dr. Shigemi Hitomi for his help with the bacterial analysis (multilocus sequence typing and deduced amino acid sequence).

References
1. Agrawal A, Murphy TF. Haemophilus influenzae infections in the H. influenzae type b conjugate vaccine era. J Clin Microbiol 49: 3728-3732, 2011.
2. Ladhani SN, Collins S, Vickers A, et al. Invasive Haemophilus influenzae serotype e and f disease, England and Wales. Emerg Infect Dis 18: 725-732, 2012.
3. MacNeil JR, Cohn AC, Farley M, et al. Current epidemiology and trends in invasive Haemophilus influenzae disease-United States, 1989-2008. Clin Infect Dis 53: 1230-1236, 2011.
4. Desi S, Jamieson FB, Patel SN, et al. The Epidemiology of invasive Haemophilus influenzae non-serotype B disease in Ontario, Canada from 2004 to 2013. PLoS One 10: e0142179, 2015.
5. Berndsen MR, Erlendsdottir H, Gottfredsson M. Evolving epide-
miology of invasive Haemophilus infections in the post-
vaccination era: results from a long-term population-based study. Clin Microbiol Infect 18: 918-923, 2012.
6. Hagiya H, Murase T, Naito H, Hagioka S, Morimoto N. Severe soft tissue infection of the lower extremity caused by Haemophilus influenzae (serotype f, biotype II) in an adult patient. Intern Med 51: 1783-1787, 2012.
7. Hoshino T, Hachisu Y, Kikuchi T, et al. Analysis of Haemophilus influenzae serotype f isolated from three Japanese children with invasive H. influenzae infection. J Med Microbiol 64: 355-358, 2015.
8. Usui Y, Kakuta R, Araki M, et al. Adult-onset invasive Haemophi-
lus influenzae type f caused by acute lower leg cellulitis. Intern Med 55: 1811-1813, 2016.
9. Falla TJ, Crook DW, Brophy LN, et al. PCR for capsular typing of Haemophilus influenzae. J Clin Microbiol 32: 2382-2386, 1994.
10. Meats E, Feil EJ, Stringer S, et al. Characterization of encapsu-
lated and noncapsulated Haemophilus influenzae and determina-
tion of phylogenetic relationships by multilocus sequence typing. J Clin Microbiol 41: 1623-1636, 2003.
11. Ubukata K, Shibasaki Y, Yamamoto K, et al. Association of amino acid substitutions in penicillin-binding protein 3 with beta-lactam resistance in beta-lactamase-negative ampicillin-resistant Haemophilus influenzae. Antimicrob Agents Chemother 45: 1693-1699, 2001.
12. Giurfa M, Daprai L, Cardines R, et al. Carriage of Haemophilus influenzae in the oropharynx of young children and molecular epi-
demiology of the isolates after fifteen years of H. influenzae type b vaccination in Italy. Vaccine 33: 6227-6234, 2015.
13. Fleury C, Su YC, Hallström T, et al. Identification of a Haemophi-
lus influenzae factor H-Binding lipoprotein involved in serum re-
sistance. J Immunol 192: 5913-5923, 2014.
14. Ladhani S, Slack MP, Heath PT, et al. Invasive Haemophilus influenzae disease, Europe, 1996-2006. Emerg Infect Dis 16: 455-463, 2010.
15. Resman F, Ristovski M, Ahl J, et al. Invasive disease caused by *Haemophilus influenzae* in Sweden 1997-2009; evidence of increasing incidence and clinical burden of non-type b strains. Clin Microbiol Infect 17: 1638-1645, 2011.

16. Parke JG. Meningitis caused by type F *Hemophilus influenzae*; report of a case with recovery. J Pediatr 1945 27: 567-571, 1945.

17. Wagener WC, Myerowitz RL, Dulabon GM. Lethal meningocerephalitis and septicemia caused by *Haemophilus influenzae* type f in an adult with multiple myeloma. J Clin Microbiol 14: 695-696, 1981.

18. Klein BL, Boxerbaum B, Aronoff SC. *Hemophilus influenzae* type f meningitis in an adolescent. Pediatr Emerg Care 1: 145-146, 1985.

19. Meier FP, Waldvogel FA, Zwahlen A. Role of splenectomy in the pathogenesis of *Haemophilus influenzae* type f meningitis. Eur J Clin Microbiol 4: 598-600, 1985.

20. Ubukata K, Chiba N, Morozumi M, Iwata S, Sunakawa K. Working Group of Nationwide Surveillance for Bacterial Meningitis. Longitudinal surveillance of *Haemophilus influenzae* isolates from pediatric patients with meningitis throughout Japan, 2000-2011. J Infect Chemother 19: 34-41, 2013.

21. Tsang RSW, Shuel M, Whyte K, et al. Antibiotic susceptibility and molecular analysis of invasive *Haemophilus influenzae* in Canada, 2007 to 2014. J Antimicrob Chemother 72: 1314-1319, 2017.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).