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Meningitis due to *Haemophilus influenzae* - a case report

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ABSTRACT:

— ***Background:*** We describe a case of meningitis due to *Haemophilus influenzae* detected by BioFire FilmArray Meningitis/Encephalitis Polymerase Chain Reaction (PCR) panel on a cerebral spinal fluid sample collected from a repeated lumbar puncture.

— ***Case Report:*** A 69-year-old female with a history of diabetes mellitus was admitted to another hospital 5 months prior with altered mental status. After a lumbar puncture, she was diagnosed with meningitis and was treated with antimicrobials. The patient then presented to our hospital, and the initial lumbar puncture was unable to identify any specific organism. Another lumbar puncture was performed in order to be able to diagnose her with meningitis due to *Haemophilus influenzae*. The patient was, therefore, treated with ceftriaxone for 14 days, achieving a complete resolution of her symptoms.

— ***Conclusions:*** This case highlights the clinical significance of repeating the lumbar puncture in cases of diagnostic uncertainty and discusses the likelihood of false-positive results on the BioFire FilmArray PCR panel and the importance of correlating diagnostic sensitivity with clinical manifestations.

— ***Keywords:*** *Haemophilus influenzae*, Meningitis, BioFire FilmArray Meningitis/Encephalitis PCR panel.

BACKGROUND

Haemophilus influenzae (H. influenzae) is a gram-negative coccobacillus, an otherwise benign commensal organism of the human nasopharyngeal flora. There are several serotypes within the species with the propensity to cause disease in humans, with 6 main serotypes labeled from "a" to "f"[1]. *H. influenzae* serotype b [Hib] is the most virulent, due to its ability to cause invasive multisystem disease. This is largely due to its polysaccharide capsule, the driving force of its virulence. Hib, non-b, and non-typeable *H. influenzae* are responsible for more than 90% of systemic diseases, which include meningitis, bacteremia or sepsis, epiglottitis, pneumonia, septic arthritis, osteomyelitis, pericarditis, cellulitis[2].

According to the WHO[3], *H. influenzae* poses a significant public health concern in many parts of the world, with as many as three million cases of serious disease every year, manifesting primarily as pneumonia and meningitis in the young. Patients ≥ 65 years of age with invasive *H. influenzae* disease have higher case-fatality ratios than children. Up to 20% of patients who survive Hib-meningitis have long-term neurological sequelae, such as hearing loss[4].

The following is a case report detailing the diagnosis of bacterial meningitis in a patient who tested positive for *H. influenzae* through PCR on a repeat cerebrospinal fluid (CSF) sample.

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CASE PRESENTATION

A 69-year-old Caucasian female born in the United States with anecdotal reports of childhood vaccinations, a significant past history of Chronic Obstructive Pulmonary Disease on baseline 3 liters/minute home oxygen (O_2), diabetes mellitus type 2 on insulin and metformin, hypertension, gout, hyperlipidemia, ischemic stroke with residual left-sided deficits, hepatomegaly with severe steatosis, presented in March 2023 with acute onset of nausea, vomiting and altered mental status (AMS) for 2 hours. No known sick contacts and no significant travel nor exposure history were registered.

Five months prior to this admission, in October 2022, the patient had been admitted to a neighboring hospital with nausea, vomiting, AMS, headache, and photophobia concerning bacterial meningitis. She was febrile with a leukocytosis of 21.2×10^9/L (range 4.0-11.5×10^9/L). Head Computed Tomography (CT) without contrast was negative for acute intracranial processes. Meningitis was high on the differential, and she was started on empiric therapy (adjusted for creatinine 0.8 mg/dl, eGFR 80 ml/min, body weight 111 kg) with IV vancomycin 1,250 mg q 12 hour (hr) (goal trough level 15-20), IV meropenem 2 gm q 12 hr, IV acyclovir 1,150 mg q 8 hr, and IV dexamethasone 10 mg q 12 hr. A lumbar puncture (LP) was obtained after 48 hours of antibiotics. CSF studies supported a laboratory diagnosis of bacterial meningitis; however, no organism was identified on the CSF BioFire FilmArray Meningitis/Encephalitis PCR panel (BioFire ME/EN PCR panel, bioMérieux, Salt Lake City, Utah, USA) nor on the CSF gram stain and culture. CSF studies are described in Tables 1, 2, and 3. Additional CSF studies were negative for *Cryptococcus* Ag, Venereal Disease Research Laboratory (VDRL), West Nile Virus (WNV) IgM and IgG antibody (Ab), Varicella Zoster Virus (VZV) PCR, and Herpes Simplex Virus (HSV) 1 and 2 PCR. Blood cultures and serum Human Immunodeficiency Virus (HIV) 1 and 2 Ab screens were negative. Urine studies were negative for urinary tract infection and S*treptococcus pneumoniae* antigen (Ag) test. Due to clinical improvement in mentation on empiric antimicrobial therapy, bacterial meningitis remained the leading diagnosis, and IV acyclovir was discontinued. Due to psychosis, meropenem was de-escalated to IV ceftriaxone 2 gm q 12 hr, of which she completed a fourteen-day course on October 18, 2022.

On day 1 of her second admission in March 2023, the patient was febrile again with 103.2°F, tachycardic but otherwise hemodynamically stable on home oxygen requirements. Physical exam was notable for left-sided residual weakness attributed to a known history of stroke. The patient underwent an urgent stroke workup with CT head and Magnetic Resonance Imaging (MRI) of the brain for acute stroke without contrast, both of which showed no acute intracranial abnormality. The patient was evaluated by the on-call stroke neurologist, who found the patient's clinical and imaging findings to be inconsistent with acute stroke.

Table 1. CSF and serum laboratory values from previous and current admission.

1st hospitalization (10/04/22 – 10/10/22)	**06/10/2022**		**2nd hospitalization (03/14/23 – 03/22/23)**	**15/03/2023**	**21/03/2023**	
CSF contents [total 1.5 mL]	Result/unit	Reference range	CSF contents [total 14 ml]	Result/unit	Result/unit	Reference range
Glucose	97 mg/dL	[40-70 mg/dL]	Glucose	123 mg/dL	96 mg/dL	[40-70 mg/dL]
Protein	91 mg/dL	[12-60 mg/dL]	Protein	95.6 mg/dL	89.9 mg/dL	[15-45 mg/dl]
Red Blood Cells (RBC)	31/cmm	[0-0/cmm]	RBC	0/cmm	10,000/cmm	[0-0/cmm]
White Blood Cells (WBC)	78/cmm	[0-9/cmm]	WBC	682/cmm	18/cmm	[0-5/cmm]
Appearance	Clear, colorless	[Clear, colorless]	Appearance	Clear, colorless	Hazy, Red	[Clear, colorless]
Opening pressure	Mild, 17 cm H_2O	[7-18 cm H_2O]	Opening pressure	N/A	N/A	N/A

Table 2. CSF cell count differential.

CSF cell differentials	**06/10/2022**	**Reference range**	**CSF Cell differentials**	**15/03/2023**	**21/03/2023**	**Reference range**
Neutrophil	78%		Neutrophil	85%	50%	<10%
Lymphocyte	7%		Lymphocyte	5%	47%	--
Monocyte	15%		Monocyte	10%	3%	--
Concurrent Serum glucose	152 mg/dl	[80-115 mg/dl]	Concurrent Serum glucose	162 mg/dl	174 mg/dl	[70-105 mg/dL]

Table 3. CSF gram stain and culture results.

CSF cultures	06/10/2022	CSF Cultures	15/03/2023	21/03/2023
CSF Gram stain and culture	WBC 2+, no organisms seen, no growth at 3 days.	CSF Gram stain and culture.	Many WBC, no organisms seen, no growth in 7 days.	Many WBC, Many RBC, no organisms seen, no growth in 7 days.
CSF Fungal culture	No yeast or mold isolated after 4 weeks.	CSF Fungal culture	No fungus isolated at 4 weeks, no encapsulated yeast seen on India ink.	No encapsulated yeast seen on India ink.
CSF AFB smear and culture	Not performed.	AFB Culture and smear	Smear negative for acid-fast bacilli, Culture negative after 42 days of incubation.	Not performed.

Laboratory data on admission were significant for leukocytosis of 20.8×10^9/L with left shift (range 3.8-10.8×10^9/L), sodium 130 mmol/L, glucose 575 mg/dl, anion gap 19, creatinine 1.3 mg/dl, eGFR 41 (baseline 0.7-1.0, eGFR > 60), lactic acid 8.0 mmol/L, hemoglobin A1c 10.2%. Urinalysis was notable for glucosuria, though no ketonuria, pyuria, or bacteriuria. Limited respiratory panel was negative for Influenza A/B, SARS Coronavirus-2, and Respiratory Syncytial Virus. Diabetic ketoacidosis (DKA) protocol was initiated, and she was admitted for AMS workup. She was given a single dose of 1 gm IV cefepime and 500 mg IV azithromycin for possible aspiration pneumonia, although the chest radiograph showed no pulmonary infiltrate.

Although there was no nuchal rigidity on this admission, there was clinical suspicion of infectious meningitis, given her fevers and altered mentation. On day 2 of her admission, the patient started empiric therapy (adjusted for creatinine 1.2 mg/dl, eGFR 46.2 ml/min, body weight 105 kg) with IV acyclovir 700 mg q 12 hr, IV ceftriaxone 2 gm q 12 hr, IV vancomycin 1,500 mg q 24 hr (goal trough level 15-20), and IV ampicillin 2 gm q 8 hr. LP was attempted, but it was found to be inadequate; therefore, on day 3, the patient underwent another LP (results in Tables 1, 2 and 3).

Given persistent altered mentation, the Infectious Diseases team was consulted on day 4 to assist with infectious evaluation. LP studies from day 3 showed CSF glucose 123 mg/dl (in patient in DKA), concurrent serum glucose 162 mg/dl, CSF total protein 95.6 mg/dl, CSF WBC 682/cmm with 85% neutrophils, and negative meningitis/encephalitis panel. CSF and blood cultures showed no growth. There was strong suspicion for additional etiologies of meningitis: CSF *Cryptococcus* Ag, VDRL, *WNV* IgM and IgG Abs, Western equine encephalitis IgM and IgG Abs, anti-GAD65 Ab, Paraneoplastic Autoantibody Panel, and VZV PCR were negative. Serum Arbovirus Ab Panel, *Coccidioides* Ab panel, and HIV 1 and 2 Ag and Ab were also negative. IV ampicillin was discontinued due to negative Listeria on the PCR panel. Given the degree of leukocytosis with neutrophilic predominance, bacterial meningitis was strongly suspected, and IV vancomycin and IV ceftriaxone were continued. Given the concern for recurrent meningitis, IV acyclovir was continued for possible Mollaret's Syndrome. HSV Type 1 and 2 DNA PCR of the CSF was not obtained with the initial CSF studies, and a repetition of the LP was recommended. The patient's mentation returned to baseline by day 7 of treatment. LP was repeated on day 9 of admission to exclude recurrent HSV meningitis. HSV 1 and 2 PCR were negative. However, the repeated BioFire ME/EN PCR panel returned positive for *H. influenzae*.

IV Acyclovir and IV Vancomycin were discontinued, and IV ceftriaxone was continued. The patient's mentation continued to improve, and leukocytosis and fevers resolved. The patient was discharged to a skilled nursing facility to complete IV ceftriaxone for a total of 14 days.

At the outpatient follow-up, the patient was back at her baseline measurement with full symptom resolution. CSF culture did not grow *H. influenzae* and remained negative 7 days after collection. The Center for Disease Control and Prevention (CDC) was contacted, and it was determined that the patient did not meet the indicated criteria to receive the Hib vaccine. Her partner, in addition, did not meet the criteria for chemoprophylaxis with rifampin. The patient declined to perform further testing to evaluate for immunoglobulin deficiency, which could predispose patients to recurrence with meningitis.

DISCUSSION

This is a case of an elderly patient who presents with a recurrence of bacterial meningitis and tested positive for *H. influenzae* on a BioFire PCR panel obtained from a repeat LP after exposure to antibiotics.

The patient's initial CSF studies were obtained without exposure to antibiotics. *H. influenzae* was not detected on the BioFire ME/EN PCR panel or grown on CSF culture after incubation for 7 days. Given the diagnostic uncertainty of the case and our high suspicion of bacterial meningitis, a second lumbar puncture was performed, which detected *H. influenzae* on PCR. Repeat CSF cultures again did not grow *H. influenzae*. However, the patient had several days of exposure to empiric antibiotics at the time of the repeat workup. Sending additional CSF studies might have been helpful in diagnosing bacterial meningitis. In fact, a study by Sharda et al[5] has shown that a point-of-care CSF dipstick test combining leucocyte esterase, protein, and glucose has good sensitivity for triaging patients with suspected bacterial meningitis in the Emergency Department[5].

Our team queried the meaning of these results. First, *H. influenzae* was not detected on the initial CSF workup. Was its detection on repeat LP attributable to the sensitivity of the BioFire ME/EN PCR panel, or was it a true positive? If so, why was there an absence of growth in repeated culture? Are there any clinical implications for repeating the lumbar puncture in the event of diagnostic uncertainty?

Although culture has been considered[6] to be the 'gold standard' for case confirmation, the proportion of suspect cases with positive culture is relatively low due to a variety of factors, including suboptimal storage or transportation of clinical specimens and antibiotic administration prior to specimen collection. There was no growth detected in either CSF culture. The absence of growth on the second culture could be attributable to antibiotic exposure, decreasing the yield needed to achieve growth in culture. However, the initial culture was also negative, and that was obtained prior to antibiotic exposure. A few possibilities could be at play, one being the collection and processing method. It is unclear if this was an appropriate collection performed in the Emergency Department. Specimen handling is a fragile process, which can disrupt the results if certain conditions for processing are not met.

The BioFire ME/EN PCR panel has a sensitivity of 94.2% and a specificity of 99.8%. Several studies[7] in literature have demonstrated that real-time is more accurate than CSF culture in the detection of meningitis. The initial PCR did not detect a pathogen on the BioFire ME/EN panel, but the repeated panel did. According to a study by Wu et al[7], a false positive is a known phenomenon with the BioFire ME/EN panel, specifically for *H. influenzae*. If this was a false positive, it would explain why neither CSF culture grew a pathogen. A recent study by Zanella et al[8] highlighted the need for caution in positive results for *H. influenzae* with the BioFire ME/EN panel and whether it should always be interpreted with clinical manifestation, CSF analysis, and other microbiological results[8].

Repeat lumbar puncture in this case was done due to high suspicion of bacterial meningitis. However, according to guidelines[9] published in 2004, repeat lumbar puncture is indicated for any patient who has not responded clinically after 48 hours of appropriate antimicrobial therapy, neonate with meningitis due to gram-negative bacilli to document CSF sterilization as the duration of antimicrobial therapy is determined by CSF results, and in patients with CSF shunt infection. However, a recent study performed by Costerus et al[10] in 2016 pointed fingers in the direction of possible other indications for repeat lumbar puncture, such as diagnostic uncertainty after the first lumbar puncture, to rule out relapsing infection in patients who deteriorate after 48 hours of adequate antibiotic therapy and therapeutically in patients with hydrocephalus.

CONCLUSIONS

Detection of an organism is sometimes challenging in patients with suspected meningitis. This case supports the need for repeated LP in situations when clinical suspicion for bacterial meningitis is high and when the initial workup is negative

Conflict of Interest:
The authors declare that they have no conflict of interest.

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All the authors contributed to the clinical evaluation of the case and the manuscript's drafting.

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