



Case report

Haemophilus parainfluenzae endocarditis with multiple cerebral emboli in a pregnant woman with coronavirusAlicia De Castro^{a,*}, Mohammad Abu-Hishmeh^b, Ibrahim El Hussein^c, Lisa Paul^b^a Department of Internal Medicine, Westchester Medical Center, New York Medical College, Valhalla, NY, United States^b Department of Internal Medicine, Division of Pulmonary and Critical Care, Westchester Medical Center, New York Medical College, Valhalla, NY, United States^c Department of Internal Medicine, Division of Pulmonary and Critical Care, University Hospital, Rutgers University, Robert Wood Johnson Medical School, New Brunswick, NJ, United States

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Background

Haemophilus parainfluenzae, one of the HACEK organisms including *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species organisms, is an uncommon cause of infective endocarditis (IE), with 0.8–6.0% of cases of IE caused by one of the HACEK organisms [1–3]. Complications from *Haemophilus parainfluenzae* endocarditis (HE) can be severe, but it is also notable for having a generally favorable prognosis if appropriate treatment is initiated [4–6]. This remains a challenge because diagnosis can be delayed given the protean manifestations of endocarditis, and the slow-growing characteristics of *Haemophilus parainfluenzae*. We describe a patient with HE who presented with fever and was found to have coronavirus infection. She was treated symptomatically for viral respiratory infection but was later found to have multiple septic intracranial emboli.

Case presentation

A 34-year-old woman in her 30th week of pregnancy with a medical history significant for autoimmune thyroiditis and mitral regurgitation presented with a 4 day history of intermittent fevers (maximal temperature of 104 °F), chills, generalized fatigue, myalgias, post-nasal drip and worsening bi-frontal and retro-orbital headaches. Her prenatal course had been uncomplicated. She had no prior surgeries, no recent dental procedures, and denied intravenous drug use. She was seen at an urgent care center

and empirically treated with oseltamivir 75 mg every 12 h. Fevers persisted and she was admitted to an outside hospital and treated empirically with intravenous vancomycin 1 g every 12 h and cefepime 2 g every 8 h. She was transferred to our hospital for further evaluation and management.

On admission, her temperature was 99.1 °F, pulse rate 100 beats per minute, respiratory rate 18 per minute, blood pressure 100/48 mmHg. She was awake, alert, and fully oriented, and denied neck stiffness. On examination, she had a holosystolic murmur, and her chest was clear to auscultation. Skin examination revealed no rashes. Neurological exam showed no focal deficits and no meningeal signs. Evaluation revealed a leukocyte count of 7.8 k/mm³, hemoglobin 9.6 g/dl, platelet count 43 k/mm³, and normal liver enzymes. Respiratory multiplex PCR was positive for coronavirus. She was managed with supportive care for viral respiratory infection, and antimicrobials were discontinued.

High grade fevers persisted, and antimicrobials including vancomycin 1 g every 12 h and cefepime 2 g every 8 h were resumed. Blood cultures remained negative. On the fourth day of admission, her mental status declined, associated with worsening headache. She exhibited hyperreflexia on examination, but no meningeal signs, papilledema, or focal neurological deficits. Given her coronavirus infection, hyperreflexia, and the development of confusion, computed tomography (CT) of the brain was performed. CT of the brain showed no acute pathology, however there was an incidental finding of a cystic structure extending from the right cerebello-pontine angle to the foramen magnum that precluded obtaining a lumbar puncture. Empiric treatment for meningitis-encephalitis with broad-spectrum antimicrobials and antivirals was started, including vancomycin 1 g every 12 h, ceftriaxone 2 g every 12 h, ampicillin 2 g every 4 h, and acyclovir 700 mg every 8 h. Magnetic resonance imaging (MRI) of the brain was attempted to

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better evaluate the cystic lesion and to evaluate for a possible dural venous sinus thrombosis, but the patient developed acute respiratory distress and the study was not completed. Chest radiography demonstrated pulmonary edema and congestion. Trans-thoracic echocardiography (TTE) showed normal left ventricular function, normal ejection function, reduced respiratory variation of the inferior vena cava consistent with a volume overloaded state, posterior mitral leaflet prolapse, moderate thickening of the mitral valve leaflets, moderate mitral regurgitation, but no vegetation, as shown in Fig. 1a.

On the fifth hospital day, blood cultures demonstrated gram-negative bacilli. Cultures from the outside hospital were reported positive for *Haemophilus parainfluenzae*. Her antimicrobial therapy was narrowed to ceftriaxone 2 g every 24 h. MRI of the brain (Fig. 2a and b) showed multiple subcentimeter foci within the bilateral frontoparietal regions, left occipital lobe, and bilateral cerebellar hemispheres consistent with septic emboli and thromboembolic infarcts. A trans-esophageal echocardiogram (TEE) was recommended, however the patient refused given the risk of vocal cord injury on intubation. A repeat TTE on day 10 (Fig. 1b) then revealed a vegetation on the mitral valve measuring $1.4 \times 1.3 \times 0.8$ cm. Given her multiple cranial emboli and the presence of a large vegetation after embolization, the patient was deemed high risk for further embolic complications. The patient then underwent emergent Caesarian delivery followed by mitral valve repair. Intra-operative findings included large friable vegetations on the mitral valve and a thrombus on the posterolateral papillary muscle. Her post-operative course was uncomplicated. She remained afebrile and her clinical status improved, with normal mentation and normal cardiopulmonary function. She was discharged home to complete a four-week course of intravenous ceftriaxone.

Discussion

Haemophilus parainfluenzae, a gram-negative coccobacilli that is found in the oropharyngeal tract, is one of the HACEK (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*) organisms, and most often presents sub-acutely, with a median duration of 19 days of symptoms before diagnosis [7].

The HACEK organisms are a rare cause of IE, accounting for 0.8–6% of IE cases based on population studies [1–3], with significant regional variations seen on a multinational cohort, which showed HE in 0.5% of IE cases in North America [8].

Diagnosis of HACEK endocarditis remains a challenge because of its variable presentation and the slow-growing characteristics of the organisms. Here, the patient did not present with classic bacteremia and fever with peripheral embolic or vasculitic symptoms. Blood cultures were initially negative, yielding growth of gram-negative bacteria only on the fifth day of incubation. Additionally, a viral respiratory tract infection with subsequent neurological involvement had been initially suspected because of the worsening headaches and hyperreflexia in the setting of positive coronavirus infection testing and upper respiratory symptoms, further complicating the diagnosis.

Imaging also plays a vital role in diagnosing IE. One of its major diagnostic criteria hinges on echocardiographic evidence of an oscillating intracardiac mass or vegetation, an annular abscess, prosthetic valve partial dehiscence, or new valvular regurgitation [9]. Here, the initial TTE demonstrated no vegetation. A recent meta-analysis on the use of echocardiography in detecting vegetations notes that TTE has a sensitivity of 61% and specificity of 94%, and as such can fail to show many vegetations that are otherwise identifiable on TEE [10]. Of interest, it has been noted that vegetations are detected in a lower percentage in HACEK endocarditis (71%) in comparison to non-HACEK endocarditis (83%), though there was no difference in the rates of mitral and aortic valve vegetations between the two populations [8]. Because there was a high clinical suspicion for IE given the patient's positive blood cultures and septic intracranial emboli, a TEE was recommended. Given the patient's occupation as a singer and her fear of damaging her vocal cords, she refused TEE and opted for a repeat TTE. A repeat TTE performed 5 days after the initial TTE showed a vegetation that was greater than 1 cm in dimension. This interval increase in size of the vegetation to the point of detectability despite antimicrobial therapy is critical, as it has been shown that this carries an increased risk of complications and the need for surgery [11].

Of note, one study involving 218 cases of IE in a single center has shown that as many as 47% of patient with IE have a neurological symptom as the presenting complaint, with up to 29% of patients developing neurological complaints within 1 week of the onset of other IE-related symptoms [12]. These neurologic manifestations include headaches, toxic encephalopathy, meningitis, brain abscess, TIA, embolic stroke, and intracranial hemorrhage. This underscores the importance of maintaining a high index of suspicion of IE in patients with HACEK bacteremia with neurological symptoms.

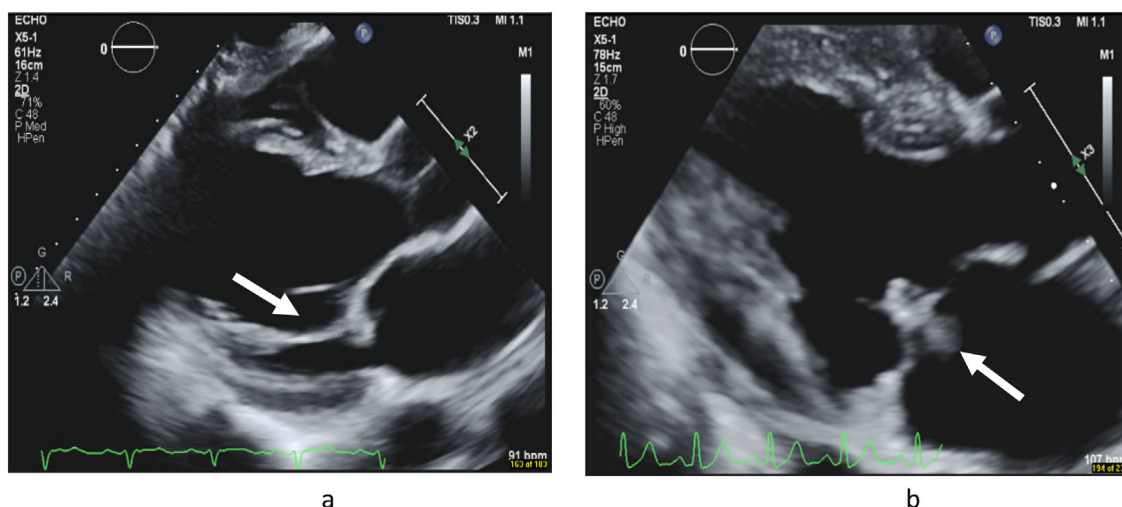


Fig. 1. a) TTE parasternal long axis view on Day 5 demonstrating thickened mitral valve leaflets. b) TTE parasternal long axis view on Day 10 demonstrating a vegetation on the mitral valve.

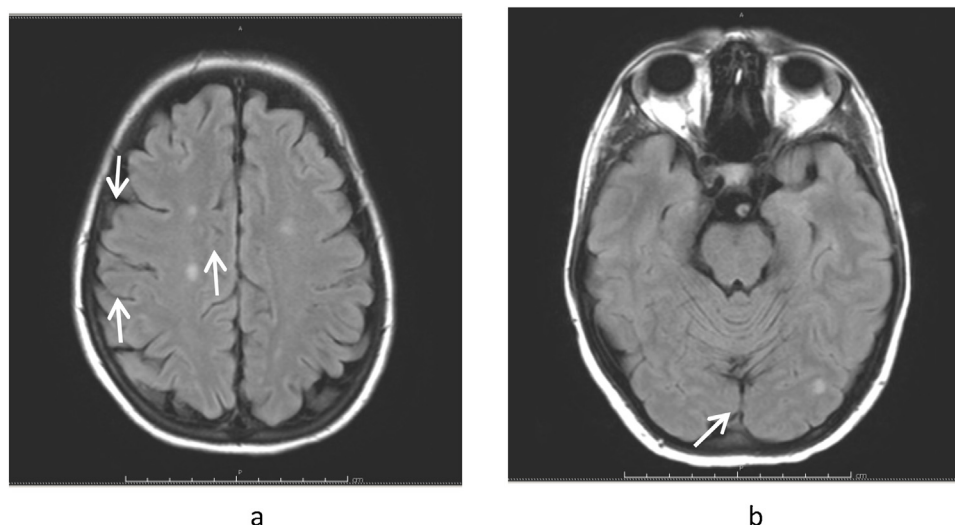


Fig. 2. a) MRI of the brain axial view showing lesions in the bilateral frontoparietal regions. b) MRI of the brain axial view showing a lesion in the left occipital lobe.

Further, it has been shown that HACEK endocarditis has a significant propensity for neurologic complications such as stroke (25%), 56% of which are embolic, and 44% due to intracranial hemorrhage [7]. The presence of neurological complications in turn is associated with a higher morbidity and doubling of median length of stay in hospital [5]. It is significant to note that many patients develop neurologic complications before antimicrobials are started [13–15], with as much as 12% of patients developing after initiating antimicrobials, the greatest risk associated with increasing vegetation size and mitral valve involvement [6]. However, the risk of embolic events to the central nervous system declines markedly after 2–3 weeks of initiation of antimicrobial therapy [4,6], falling to as low as <1.2 per 1000 patient-days after 2 weeks of therapy, declining further with time [5]. This further highlights the importance of recognizing HE and initiating appropriate antimicrobials, as infection control plays a critical role in preventing embolic events.

Conclusion

In summary, our patient's presentation reinforces that neurological symptoms may be the presenting complaint in patients with endocarditis. Clinicians should maintain a high index of suspicion for IE when encountering patients presenting with neurological complaints in the setting of fever, given the potential for cerebrovascular complications, and the improved outcomes with timely initiation of appropriate antimicrobial therapy.

Author contributions

Conception and design of study: Alicia De Castro; Mohammad Abu-Hishmeh.

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