

Cerebral spinal fluid positive pertussis encephalopathy in infants: Case reports

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Ta Anh Tuan¹ , Tran Dang Xoay¹ ,
Phung Thi Bich Thuy² and Yves Ouellette³ 

Abstract

Pertussis has re-emerged in both developed and developing countries and is an ongoing public health problem, even in countries with high rates of vaccination. Pertussis encephalopathy is a known complication of the disease, but the pathophysiology of this complication and the role of the pertussis bacteria have not been elucidated. We report three confirmed cases of pertussis infant younger than 3 months of age with neurological complications including lethargy, encephalopathy, and seizures. In each case, the cerebrospinal fluid was positive for *Bordetella pertussis* as determined by polymerase chain reaction. One patient did not survive and two were discharged with a normal neurological exam on follow-up. The cases emphasize the importance of analyzing cerebrospinal fluid in cases of pertussis-associated encephalopathy including polymerase chain reaction.

Keywords

Pertussis encephalopathy, *Bordetella pertussis*, cerebrospinal fluid, seizure

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Introduction

Whooping cough is an infectious disease that still causes epidemics with high mortality rates in both developed and developing countries.^{1,2} Encephalopathy is a rare and severe, complication of pertussis, but the cause of this condition and the association with the pertussis bacteria have not been elucidated. We present three cases of pertussis encephalopathy with positive polymerase chain reaction (PCR) to *Bordetella pertussis* suggesting an infectious cause for the encephalopathy.

Pertussis remains one of the least well-controlled vaccine-preventable diseases for which routine vaccination exists. Although most often a persistent but relatively benign respiratory illness, pertussis can result in serious consequences, such as pneumonia, seizures, encephalopathy, and death, especially among infants.

Cases presentations

We report on three cases of *Bordetella pertussis* encephalopathy with PCR positive cerebrospinal fluid (CSF). Between January 2015 and December 2019, 86 *B. pertussis* PCR positive infants were admitted to the pediatric intensive care unit (PICU) at the National Children Hospital in

Hanoi, Vietnam (Figure 1). The CSF PCR for *B. pertussis* was done in the hospital's clinical laboratory. Total nucleic acids were extracted from samples using the MagNA Pure LC 2.0 instrument with the MagNA Pure LC total nucleic acid isolation kit according to the manufacturer's instructions (Roche Diagnostics, Basel, Switzerland). 100-nucleotide segment of the Bp481 region was amplified by the use of primers as previously described.³

Case I

A non-immunized 50-day-old male presented to the emergency department with paroxysmal cough, cyanosis, fever,

¹Pediatric Intensive Care Unit, Vietnam National Children's Hospital, Hanoi, Vietnam

²Department of Biomolecular Research in Infectious Disease, Vietnam National Children's Hospital, Hanoi, Vietnam

³Department of Pediatrics, Mayo Clinic, Rochester, MN, USA

Corresponding Author:

Tran Dang Xoay, Pediatric Intensive Care Department, Vietnam National Children's Hospital, 18/879 La Thanh Street, Dong Da District, Hanoi, 10000, Vietnam.
Email: dr.trandangxoay@gmail.com



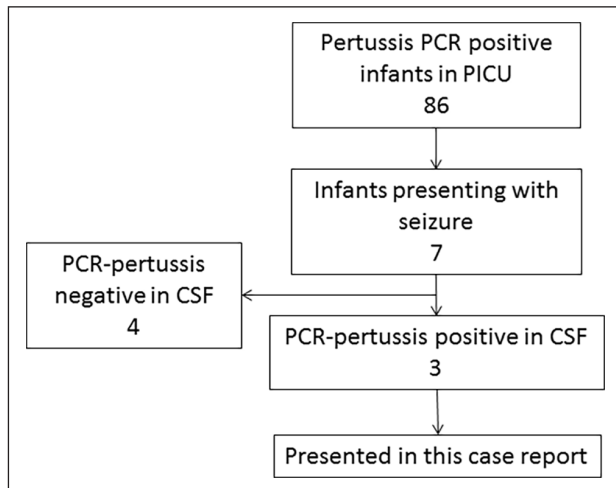


Figure 1. Flow diagram for patient inclusion criteria.

and seizures. In Vietnam, the first pertussis vaccination is scheduled at the 2 months of age. The parents were never vaccinated against pertussis as children and the mother did not receive antenatal pertussis vaccination. He had a non-eventful perinatal period and had no known risk factors for seizures. Eleven days prior to this hospitalization, he was admitted to a local hospital with a temperature of 39°C and paroxysmal coughing. He was diagnosed with pneumonia and treated with non-invasive ventilation. He had a seizure on days 8 and 11 of that admission. Because of a suspicion of meningitis, he was transferred to the emergency department of the National Children's Hospital in Hanoi. Of note, the parents were not vaccinated against pertussis. Of note, at 39 weeks gestation, the mother had a cough but did not receive antibiotics. She was later found to have a positive nasopharyngeal swab PCR for *B. pertussis* during her child's admission to the PICU. On admission to the PICU, the child was also found to have a positive nasopharyngeal swab PCR for *B. pertussis*. Additional hematological investigations found a leukocytosis $36.5 \times 10^9/L$ and lymphocytosis $13.8 \times 10^9/L$. The patient's condition deteriorated with respiratory failure, pulmonary hypertension, and status epilepticus. A lumbar puncture was performed and CSF was found to be PCR positive for *B. pertussis*. CSF tested negative by PCR for *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, Enterovirus, and Herpes simplex virus. Further analysis of the CSF was not possible due to the small sample collected. Diffusion-weighted magnetic resonance imaging (MRI) demonstrated enhancement suggesting cytotoxic edema (Figure 2). Treatments included azithromycin, mechanical ventilation, and sildenafil for pulmonary hypertension. Seizures were controlled with midazolam and valproic acid. The patient was discharged home on day 50 of hospitalization. On follow-up, he was found to be healthy with normal mental development at 22 months of age.

Case 2

A non-immunized 22-day-old female presented to a local hospital with paroxysmal cough and fever. Six days prior to hospitalization, she had multiple episodes of paroxysmal cough, vomiting, and a fever of 38.5°C. She was admitted at a local hospital with a diagnosis of pneumonia. After 3 days of treatment, her respiratory status worsened with apnea requiring intubation and mechanical ventilation. She was diagnosed with pertussis based on clinical symptoms and transferred to the emergency department at our hospital. On history, the infant had an unremarkable perinatal history with no risk factors for seizures. Her parents had never been vaccinated as children against pertussis and had not shown symptoms prior to this admission. Of note, her mother did not receive antenatal vaccination against pertussis. On admission to our hospital, the infant had a nasopharyngeal swab PCR positive for *B. pertussis*. Because of worsening her respiratory status and evidence of pulmonary hypertension, she was admitted to the PICU. She was noted to have a leukocytosis $70.3 \times 10^9/L$ and a lymphocytosis $23.6 \times 10^9/L$. She was treated with mechanical ventilation and a blood exchange transfusion for the leukocytosis. Her neurological status deteriorated and she was diagnosed with encephalopathy. A head ultrasound ruled out an intracranial hemorrhage. A lumbar puncture was performed and her CSF was PCR positive for *B. pertussis*. No further investigations were performed on the CSF. PCR was negative for other infectious causes of encephalopathy as described in Case 1. She expired on day 2 of hospitalization with dilated pupils suggesting cerebral edema and brain death.

Case 3

A 90-day-old male presented to our hospital with cyanosis, apnea, and seizure. The infant had an unremarkable perinatal period and did not have any risk factors for seizures. Two days prior to hospitalization, he had poor oral intake, lethargy, and cyanosis. He was afebrile. He was born at 30 weeks of gestation and had received one dose of DPT-HepB-Hib combine vaccine (Quinvaxem, Korea) at day 60 of age. His parents were not vaccinated against pertussis as children and were asymptomatic. His mother did not receive the pertussis vaccine during her pregnancy. A presumptive diagnosis of sepsis was made and he was transferred to the PICU. A nasopharyngeal swab PCR was positive for *B. pertussis*. The CSF was also positive for *B. pertussis* by PCR. The CSF was negative for the presence of red and white cells (normal range = <5 cells/ μL) but had an elevated protein level at 3.84 g/L (normal range = 0.4–0.8 g/L), elevated glucose 7.76 mmol/L (normal range = 3–6 mmol/L), and a normal lactate of 1.8 mmol/L (normal range = <2 mmol/L). The CSF was negative for other organisms such as *S. pneumoniae*, *H. influenzae* type B, Enterovirus, and Herpes simplex virus by PCR. The serum ammonia was normal (38 $\mu g/dL$) and serum lead level

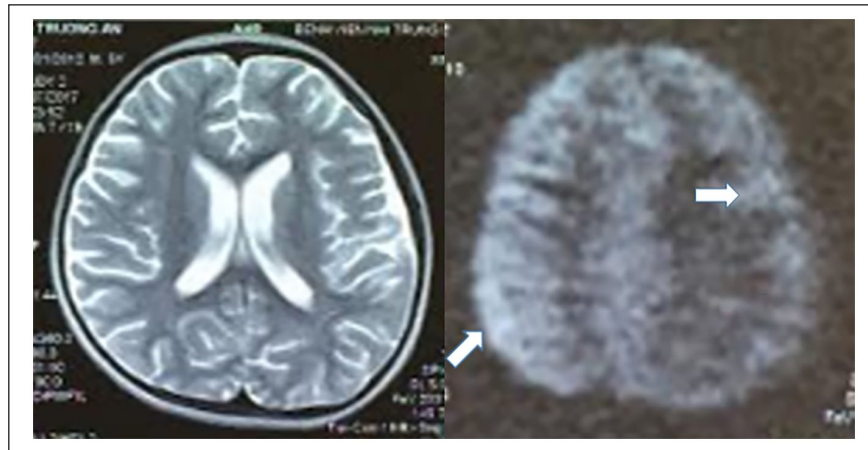


Figure 2. Brain MRI brain (left) of Case 1 with the matching showing the diffusion-weighted magnetic resonance image (right) enhancement (arrow) suggesting areas of cerebral hypoperfusion.

was normal (5.6 $\mu\text{g}/\text{dL}$). A brain MRI was normal. Seizures were treated with valproic acid. He was treated with azithromycin and improvement of his symptoms. A repeat lumbar puncture on day 10 was performed with normalization. The CSF was acellular with normal protein (1.06 g/L), glucose (2.92 mmol/L), and lactate (1.5 mmol/L). He was discharged home on day 10 of hospitalization. On follow-up at 28 months with a pediatric neurologist, he was found to have normal development.

Discussion

Encephalopathy has been well-recognized as a serious complication of pertussis and risk factor for morbidity.⁴ The etiology of the encephalopathy is unclear, but several mechanisms have been proposed including central nervous system hemorrhage, hypoxia, vascular occlusion secondary to leukocytosis, or the effects of toxins produced by *B. pertussis*.⁵ In children less than 12 months, neurological complications of pertussis such as seizures (3%), encephalopathy (0.9%), and apnea (42%–51%) have been reported.⁶ All three patients reported here had documented pertussis with neurological symptoms such as seizures, apnea, lethargy, and cerebral edema.

A previous report of pertussis encephalopathy failed to demonstrate *B. pertussis* by culture or PCR analysis.⁷ Our report suggests that the presence of *B. pertussis* in the CSF may contribute to the encephalopathy. The elevated CSF protein may be secondary to increased myelin protein.⁸ Others have also reported elevated CSF protein and have postulated an association with pertussis infection.⁹ There is evidence that the pertussis toxin might be the precipitating agent causing the reversible encephalopathy in a mouse model.¹⁰

A few studies have documented the neuropathology associated with pertussis encephalopathy. The brain shows non-specific alterations, notably swelling, anoxic-ischemic changes, venous congestion, and petechial hemorrhages.¹¹

MRI changes associated with pertussis encephalopathy have been reported and include encephalitis and evidence of demyelination.^{7,8} We report here on one patient with diffusion-weighted MRI demonstrating enhancement possibly related to cytotoxic edema. Early recognition of pertussis-associated encephalopathy is essential. Aggressive management of seizures, including the possibility of subclinical seizures, may improve outcomes. In addition, the potential risk of cerebral edema might affect further management.

In Vietnam, the first vaccination against pertussis is scheduled at 2 months of age, and there currently are no recommendations for vaccination against pertussis during pregnancy. Since 2012, the Advisory Committee on Immunization Practices (ACIP) recommends that pregnant women receive a dose of Tdap to increase passive humoral immunity to the newborn to prevent pertussis immediately after birth.¹² A recent systematic review and meta-analysis supports the assertion that pertussis vaccination during pregnancy provides immunogenic, safe, and effective protection in newborns against pertussis until their first dose of routine vaccination.¹³ The timing of antenatal pertussis vaccination may be critical. Immunizing against Tdap early within the third semester (27–30 + 6 weeks of gestation) maximizes the maternal antibody response and passive antibody transfer to the fetus.¹⁴ Therefore, giving the Tdap vaccine as early as possible in the 27–36 weeks of gestation window appears to be the best strategy.^{15,16}

Conclusion

We report three confirmed cases of pertussis infant younger than 3 months old with neurological complications including lethargy, encephalopathy, and seizures. The cases emphasize the importance of analyzing CSF in cases of pertussis-associated encephalopathy including PCR. Further investigations should be undertaken to improve upon the findings of this study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval to report this case series was obtained from Ethical Committee of the Vietnam National Children's Hospital (approval no. VNCH-RICH-2017-20).

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Informed consent

Written informed consent was obtained from the minors' legal guardian for the publication of any potentially identifiable data included in this article.

ORCID iDs

Ta Anh Tuan  <https://orcid.org/0000-0003-1440-1801>

Tran Dang Xoay  <https://orcid.org/0000-0002-7152-0172>

Yves Ouellette  <https://orcid.org/0000-0003-1495-3251>

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