

## CASE REPORT

### Recurrent apnea in an infant with pertussis due to household transmission

Motoharu Ochi<sup>1</sup>, Nobuyuki Nosaka<sup>1,2</sup>, Emily Knaup<sup>2</sup>, Kohei Tsukahara<sup>2</sup>, Tomonobu Kikkawa<sup>1</sup>, Yousuke Fujii<sup>1</sup>, Masato Yashiro<sup>1</sup>, Keiji Sato<sup>2</sup>, Toyomu Ugawa<sup>2</sup>, Ayumi Okada<sup>1</sup> & Hirokazu Tsukahara<sup>1</sup>

<sup>1</sup>Department of Pediatrics, Okayama University Hospital, Okayama, Japan

<sup>2</sup>Advanced Emergency and Critical Care Medical Center, Okayama University Hospital, Okayama, Japan

#### Correspondence

Nobuyuki Nosaka, Department of Pediatrics, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. Tel: +81-86-235-7249; Fax: +81-86-221-4745; E-mail: pv702xz5@s.okayama-u.ac.jp

#### Funding Information

No sources of funding were declared for this study.

Received: 25 February 2016; Revised: 10 November 2016; Accepted: 13 November 2016

*Clinical Case Reports* 2017; 5(3): 241–245

doi: 10.1002/ccr3.765

#### Introduction

*Bordetella pertussis* infection represents a serious and sometimes lethal threat to newborns and infants, although it is rarely associated with severe disease in adults. Pertussis is a vaccine-preventable disease, but remains a significant public health threat as a reemerging infectious disease, with frequent global outbreaks [1]. In 2008, an estimated 16 million patients suffered from *B. pertussis* worldwide, resulting in 195,000 deaths [2]. Notably, incidence of the disease has increased among young adults during the last few decades. [1]. This is a critical issue because these young adults become potential sources of infection [3]. Therefore, there are growing concerns regarding the spread of *B. pertussis* to vulnerable infants.

We report the case of a four-week-old girl with recurrent episodes of apnea due to pertussis transmitted through household contacts. We aimed to review important aspects regarding the treatment and prevention of *B. pertussis* infection.

#### Key Clinical Message

*Bordetella pertussis* causes life-threatening apnea in infants. Lymphocytosis is an important clue for diagnosis and for determining the severity of pertussis. Antibiotics do not shorten or ameliorate the disease and only decrease the risk of transmission. Antepartum maternal immunization is important for preventing pertussis in infants.

#### Keywords

Apnea, Japan, pertussis, prevention, vaccine.

#### Case Report

A four-week-old, Japanese, female infant was taken to the emergency department of an outside hospital because of episodic cyanotic spells. She had been previously healthy with normal growth and was born at 39 weeks of gestation with a birth weight of 3280 g. On examination, she was noted to become motionless with facial cyanosis after coughing. Oxygen saturation (SpO<sub>2</sub>) was 72% with ambient air, and her pulse was 198 beats per minute (bpm). After vigorous stimulation, she started breathing and rapidly returned to a healthy color with a 98% SpO<sub>2</sub> with oxygen administration. She was transferred to our hospital for apnea monitoring.

Her mother and siblings also had a symptomatic nagging cough for more than 1 month. Two weeks prior to the birth of the patient, her nine-year-old brother began to cough, followed by her six-year-old sister and her 38-year-old mother. Her siblings had completed a series of vaccinations recommended by the National Childhood Immunization Program in Japan [4]. These vaccinations

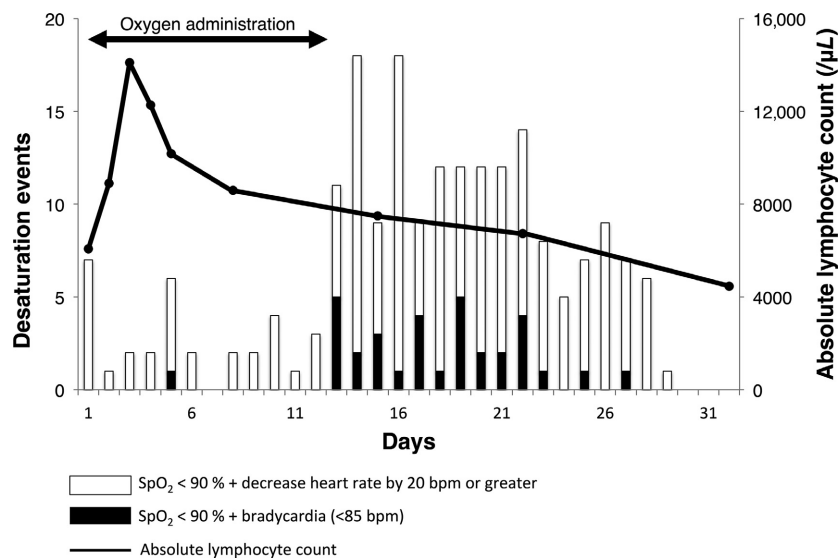
included four doses of diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at 7, 9, 11, and 27 months old. Her mother has not received pertussis vaccine for at least 30 years. The patient has not been immunized.

On arrival to our hospital, the patient appeared well. Vital signs were all within the normal range; the temperature was 37.1°C; the blood pressure 84/42 mmHg, the pulse 150 beats per minute, the respiratory rate 38 breaths per minute, and the oxygen saturation 98% while she was breathing ambient air. She had coarse crackles on the right side of the thorax and several episodes of transient apnea which lasted approximately 10–20 sec. The white cell count on admission was 26,690 WBC/ $\mu$ L; 72.0% were neutrophils and 22.5% were lymphocytes. The C-reactive protein level was 3.29 mg/dL. A chest X-ray showed infiltration in the right lower lung. Antipertussis toxin (PT) and antinflam-entous hemagglutinin (FHA) IgG levels were negative, with values of 6 and 3 EU/mL, respectively. The assay cutoff level for negative results was 10 EU/mL for both tests.

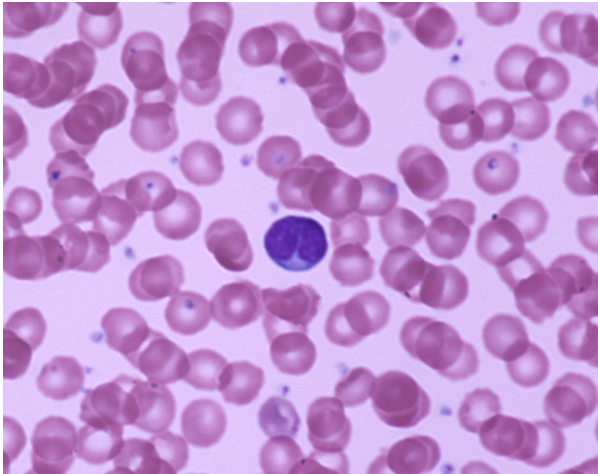
The patient was admitted to our intermediate-level unit, specially staffed to provide close cardiopulmonary monitoring. Intravenous sulbactam/ampicillin (225 mg/kg/day for 10 days) and oral azithromycin (10 mg/kg/day for 5 days) were administered. We suspected pertussis complicated by aspiration pneumonia. Anti-PT- and

anti-FHA-IgG tests were positive in the patient's mother (mother: PT-IgG, 146 EU/mL; FHA-IgG,  $\geq$ 160 EU/mL) and siblings (brother: PT-IgG, 156 EU/mL; FHA-IgG,  $\geq$ 160 EU/mL and sister: PT-IgG,  $\geq$ 160 EU/mL; FHA-IgG,  $\geq$ 160 EU/mL). The anti-PT-IgG test was considered positive at a value of  $>$ 100 EU/mL, indicating recent infection with *B. pertussis*, regardless of the immunization history. In addition, lymphocytosis was observed on day 4 after admission (maximum lymphocyte fraction of 88.0%, Fig. 1) and morphological examination of a peripheral blood smear showed numerous mature lymphocytes (Fig. 2). These findings strongly supported the diagnosis of pertussis. Furthermore, polymerase chain reaction (PCR) for *B. pertussis* was positive in a nasopharyngeal swab from the patient, with a value of 440 copies/well. The cutoff value for a positive result was 100 copies/well.

Figure 1 shows the trend of the occurrence of desaturation events and the patient's absolute lymphocyte count in our intermediate-level unit. Between desaturation events, the patient's SpO<sub>2</sub> and pulse rate were stable and were maintained at an SpO<sub>2</sub> of 98–100% with ambient air and approximately 130 bpm throughout her hospital stay. However, despite our treatment, she had repeated apnea episodes followed by desaturation and a decreased pulse rate. She also had repeated bradycardia ( $<$ 85 bpm)



**Figure 1.** Graph of the course of desaturation events and the absolute lymphocyte count. In the intermediate-level unit, the patient was fully monitored and was also monitored by her mother and the attending nurse. Each white bar shows desaturation events as detected by desaturation (SpO<sub>2</sub>  $<$ 90%) and a decrease in heart rate by  $\geq$ 20 bpm below the average heart rate for the 5 min prior to each event. Continuous oxygen administration by nasal cannula at 1–2 L/min was discontinued on the 12th hospital day, and she was carefully monitored for apnea episodes with sophisticated monitoring equipment and by healthcare professionals who could immediately intervene with resuscitation. After the discontinuation of oxygen, apparent oxygen desaturation episodes increased. However, these episodes were mild and spontaneously resolved in a short time. The frequency of episodes gradually decreased over time. The black bars show apnea events that were detected by desaturation (SpO<sub>2</sub>  $<$ 90%) and bradycardia ( $<$ 85 bpm). After the patient was transferred to the general pediatric ward on the 30-second hospital day, obvious apnea events were not observed.



**Figure 2.** Morphological examination of a peripheral blood smear. The smear shows a mature lymphocyte with scanty cytoplasm and cleaved nuclei.

episodes, despite oxygen administration by nasal cannula at 1–2 L/min, especially during the first week of hospitalization. Some apnea episodes typically occurred after consecutive bouts of coughing, and others occurred without warning (Fig. 3). Apnea episodes gradually decreased and become less severe with time. The absolute lymphocyte count reached a peak level of 14,100/ $\mu\text{L}$  on the third hospital day and then gradually decreased. The patient was discharged home on the forty-fifth hospital day. Before discharge, we instructed her parents regarding pediatric basic life support in case of repeated life-threatening apnea. At follow-up in our outpatient clinic, her mother

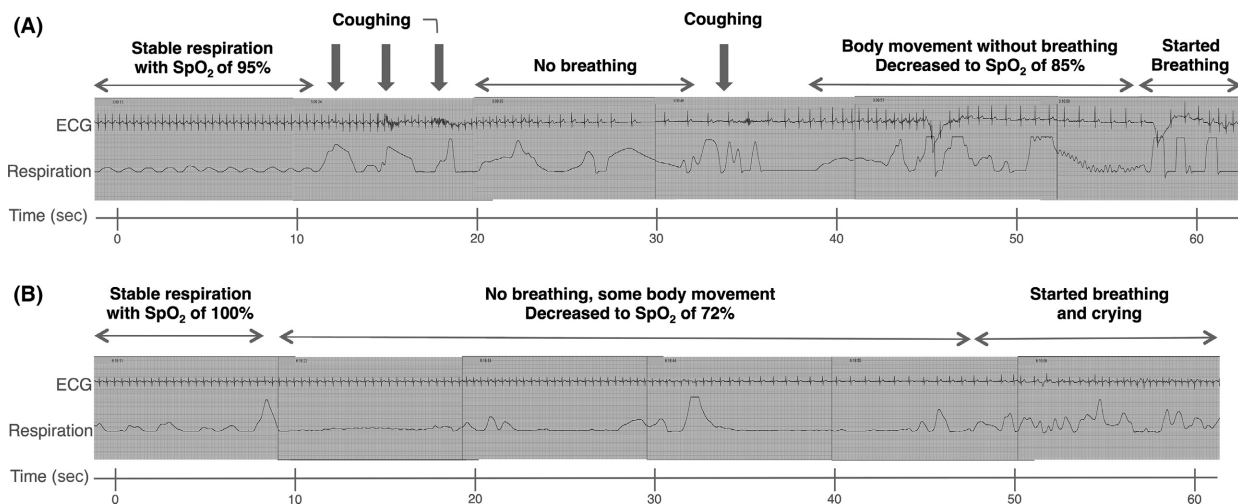
reported that she had no further apnea episodes after discharge. The total medical cost for care during hospitalization was ¥2,768,100 (approximately US \$23,000).

## Discussion

Severe cases of *B. pertussis* infection with sudden death or repeated hypoxic episodes of apnea have been reported [5, 6]. Neonates and young children, especially those who are not fully vaccinated, are more vulnerable. Recurrent apnea is a major symptom of pertussis in infants, and up to 67% of infants who are hospitalized for pertussis suffer from apnea [1]. Pertussis is not an infectious disease of the past. This illustrative case report aims to emphasize the clinical significance of pertussis, while describing various clinical clues. Also, *B. pertussis* infection may have a significant impact on medical costs. The current vaccination strategy in Japan, which lacks a recommendation for antepartum Tdap (tetanus, diphtheria, and acellular pertussis) vaccination, needs to be reconsidered.

## Diagnosis

*Bordetella pertussis* is a human-specific, Gram-negative, pleomorphic, aerobic coccobacillus that is transmitted via droplets. This microorganism grows on Bordet–Gengou agar between 35°C and 37°C. However, obtaining valuable results from a sputum culture is often difficult because of the difficulty in collecting sputum samples from infants. Serological diagnostic tests for toxins are widely used, although many critical cases of pertussis cannot be diagnosed solely with serological tests [6].



**Figure 3.** Patient's monitor record during apnea episodes. The record shows a decrease in pulse rate accompanied by a reduction in movement of the chest wall. The monitor indicates decreased oxygen saturation during this recording period. (A) An apnea episode following consecutive coughing was detected on day 14; (B) an apnea episode without warning was detected on day 10. ECG, electrocardiography.

Therefore, specific tests, such as PCR, are advisable for diagnosing pertussis. However, PCR has limited accessibility in Japan because this test is not covered by the Japanese national health insurance program.

Lymphocytosis is a major and useful diagnostic tool for pertussis infection in infants and young children [7]. However, some infants may have only mildly abnormal lymphocyte counts at the time of presentation, as seen in our case [8]. Lymphocytosis is also a good indicator of disease severity and is associated with a poor prognosis in infants, and may portend the development of pulmonary hypertension or the need for extracorporeal membrane oxygenation [7]. In addition, lymphocytes with cleaved nuclei are characteristic of *B. pertussis* lymphocytosis [9, 10] and signify mature lymphocytes as a result of the inhibition of the extravasation of lymphocytes from the blood by PT. Therefore, these signs are useful diagnostic tools for the diagnosis of *B. pertussis* infection, especially until the results of other specific tests become available.

### Clinical Course

We experienced a case of *B. pertussis* infection with a fairly typical course. Once infants develop apnea with pertussis, the usual course is that they continue to have recurrent apnea. These episodes of recurrent apnea often occur for a prolonged period, with a median duration of 19 days (range: 1–76 days) [11]. Although numerous virulence factors of *B. pertussis*, such as PT, have been studied, the precise mechanisms underlying apnea caused by *B. pertussis* infection have not been identified [12]. Therefore, in the clinical management of patients with repeated episodes of apnea, patient monitoring and diagnostic studies for possible *B. pertussis* infection are important.

### Treatment

Antibiotic treatment is not effective in treating recurrent apnea associated with *B. pertussis* infection or in shortening the duration of the infection. Antibiotic treatment

only reduces the risk of disease transmission to others. A five-day course of azithromycin is recommended as the first-line therapy for treating pertussis [8]. No effective treatment has been established for repetitive apnea caused by pertussis. Therefore, this disease needs to be carefully monitored and managed in infants.

### Problems with the Immunization Program in Japan

Our finding of an infant with recurrent apnea in whom *B. pertussis* was contracted from her siblings and her mother indicates problems in the current vaccine program in Japan. As of 2016, the National Childhood Immunization Program in Japan recommended that diphtheria, tetanus, acellular pertussis, and inactivated polio vaccine (DTaP-IPV) be administered three times from the age of 3 months. This should be followed by a booster administered between 12 and 18 months after the third dose of DTaP-IPV [4]. No additional vaccination is officially recommended after the booster shot for pertussis, despite the knowledge that the protective effect of DTaP lasts only for a maximum of 3 years after the booster, assuming 85% vaccine efficacy [13]. Table 1 shows the immunization schedules against pertussis in several countries, including Japan [4, 14–16]. The Japanese schedule requires fewer injections than that of other developed countries and does not cover immunization for school-age children and young adults. Japan should require the early introduction of Tdap vaccination, which contains less diphtheria and pertussis toxins than DTaP, for adolescents and adults.

Recent multiple epidemiological studies have suggested that antepartum maternal vaccination can reduce pertussis infection in infants in a cost-effective manner [1, 17–19]. A study in England showed that the antepartum efficacy of Tdap is >90% with a strong reduction in laboratory-confirmed infant pertussis cases and hospital admissions for pertussis [20]. Our case might have been prevented if Japan had introduced a well-developed vaccination program. We believe that serious consideration is necessary for requiring

**Table 1.** Recommended vaccination schedules against pertussis for children in the United States, Canada, Germany, and Japan.

	First	Second	Third	Fourth	Fifth	Sixth
USA	DTaP 2 months	DTaP 4 months	DTaP 6 months	DTaP 15–18 months	DTaP 4–6 years	Tdap 11–12 years
Canada	DTaP 2 months	DTaP 4 months	DTaP 6 months	DTaP 12–23 months	DTaP or Tdap 4–6 years	Tdap 14–16 years
Germany	DTaP 2 months	DTaP 3 months	DTaP 4 months	DTaP 11–14 months	Tdap 5–6 years	Tdap 9–17 years
Japan	DTaP three times From 3 months, at 3- to 8-week intervals			DTaP 12–18 months after the last shot	None	None

DTaP: diphtheria, tetanus, and acellular pertussis vaccine; Tdap: tetanus, diphtheria, and acellular pertussis vaccine; USA: United States of America.

additional pertussis vaccination, not only for children, but also for adolescents and adults in Japan.

## Acknowledgments

The authors would like to thank Dr. Takaaki Tanaka, Dr. Ippei Miyata, Professor Takashi Nakano, and Professor Kazunobu Ouchi at Kawasaki Medical University for their help with diagnostic PCR. The authors declare no financial support for this report.

## Conflict of Interest

None declared.

## Consent

Written informed consent was obtained from the parents for publication of this case report. A copy of written consent is available for review by the editor of this journal.

## Authorship

MO and NN: drafted the manuscript and contributed to treating the patient. EK: contributed to treating the patient and critically revised and edited the manuscript. KT, TK, YF, MY, KS, TU, and AO: contributed to treating the patient. HT: critically revised and edited the manuscript. All authors have read and approved the final manuscript.

## References

- Kilgore, P. E., A. M. Salim, M. J. Zervos, and H. J. Schmitt. 2016. Pertussis: microbiology, disease, treatment, and prevention. *Clin. Microbiol. Rev.* 29:449–486.
- Black, R. E., S. Cousens, H. L. Johnson, J. E. Lawn, I. Rudan, D. G. Bassani, et al. 2010. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 375:1969–1987.
- Wendelboe, A. M., E. Njamkepo, A. Bourillon, D. D. Floret, J. Gaudelus, M. Gerber, et al. 2007. Transmission of *Bordetella pertussis* to young infants. *Pediatr. Infect. Dis. J.* 26:293–299.
- Japan Pediatric Society. 2014. Vaccination Schedule Recommended by the Japan Pediatric Society. Available at [https://http://www.jpeds.or.jp/uploads/files/JPS\\_Vaccine\\_Schedule\\_English\\_20140317.pdf](https://http://www.jpeds.or.jp/uploads/files/JPS_Vaccine_Schedule_English_20140317.pdf) (accessed August 9, 2016).
- Southall, D. P., M. G. Thomas, and H. P. Lambert. 1988. Severe hypoxaemia in pertussis. *Arch. Dis. Child.* 63:598–605.
- Heininger, U., K. Stehr, G. Schmidt-Schlapfer, R. Penning, R. Vock, W. Kleemann, et al. 1996. *Bordetella pertussis* infections and sudden unexpected deaths in children. *Eur. J. Pediatr.* 155:551–553.
- Rocha, G., F. Flor-de-Lima, P. Soares, H. Soares, S. Pissarra, E. Proenca, et al. 2013. Severe pertussis in newborns and young vulnerable infants. *Pediatr. Infect. Dis. J.* 32:1152–1154.
- American Academy of Pediatrics. 2015. Pertussis (Whooping Cough). Pp. 608–621 in D. W. Kimberlin, M. A. Jackson and S. S. Long, eds. *Red Book: 2015 Report of the Committee of Infectious Diseases*, 30th ed. American Academy of Pediatrics, Elk Grove Village, IL.
- Pandey, S., and N. Cetin. 2013. Peripheral smear clues for *Bordetella pertussis*. *Blood* 122:4012.
- Funaki, T., and I. Miyairi. 2015. Lymphocytosis in a baby with pertussis. *Lancet Infect. Dis.* 15:130.
- Tozzi, A. E., L. Rava, M. L. Ciofi degli Atti, S. Salmaso, and Progetto Pertosse Working Group. 2003. Clinical presentation of pertussis in unvaccinated and vaccinated children in the first six years of life. *Pediatrics* 112:1069–1075.
- Hewlett, E. L., D. L. Burns, P. A. Cotter, E. T. Harvill, T. J. Merkel, C. P. Quinn, et al. 2014. Pertussis pathogenesis—what we know and what we don't know. *J. Infect. Dis.* 209:982–985.
- McGirr, A., and D. N. Fisman. 2015. Duration of pertussis immunity after DTaP immunization: a meta-analysis. *Pediatrics* 135:331–343.
- Vaccines gov. 2016. Recommended Immunization Schedule for Persons Aged 0 Through 18 Years. Available at [http://www.vaccines.gov/who\\_and\\_when/infants\\_to\\_teen/](http://www.vaccines.gov/who_and_when/infants_to_teen/) (accessed August 9, 2016).
- Public Health Agency of Canada. 2013. Recommended Immunization Schedules. Available at <http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-12-eng.php - tab 1> (accessed August 9, 2016).
- Wiese-Posselt, M., C. Tertilt, and F. Zepp. 2011. Vaccination recommendations for Germany. *Dtsch. Arztebl. Int.* 108:771–779; quiz 780.
- Amirthalingam, G., N. Andrews, H. Campbell, S. Ribeiro, E. Kara, K. Donegan, et al. 2014. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet* 384:1521–1528.
- Atkins, K. E., M. C. Fitzpatrick, A. P. Galvani, and J. P. Townsend. 2016. Cost-effectiveness of pertussis vaccination during pregnancy in the United States. *Am. J. Epidemiol.* 183:1159–1170.
- Sartori, A. M., P. C. de Soarez, E. G. Fernandes, L. C. Gryninger, J. Y. Viscondi, and H. M. Novaes. 2016. Cost-effectiveness analysis of universal maternal immunization with tetanus-diphtheria-acellular pertussis (Tdap) vaccine in Brazil. *Vaccine* 34:1531–1539.
- Dabrera, G., G. Amirthalingam, N. Andrews, H. Campbell, S. Ribeiro, E. Kara, et al. 2015. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012–2013. *Clin. Infect. Dis.* 60:333–337.