



Brief Report

Parainfluenza virus type 3 outbreak in a neonatal intensive care unit

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Abstract Parainfluenza virus (PIV) is a respiratory pathogen in young children and is second only to the respiratory syncytial virus (RSV) as a cause of lower respiratory tract infection. PIV type 3 (PIV3) is the most severe. Herein we describe an outbreak of PIV3 in three infants in a neonatal intensive care unit. They were diagnosed on virus culture from pharyngeal swabs. We prevented the spread of the virus using standard infection control procedures and isolation of the symptomatic infants. One infant had severe chronic lung disease and was complicated with recurrent wheezing for a long time. Because RSV and PIV have many structural, pathogenic, epidemiologic, and clinical similarities, we speculate that PIV infection causes recurrent wheezing, as observed with RSV infection. Therefore, physicians must consider recurrent wheezing at the time of treatment of PIV infection early in life.

Key words chronic lung disease, parainfluenza virus type 3, recurrent wheezing.

Human parainfluenza virus (PIV) types 1, 2, 3, and 4 are primarily known as respiratory pathogens in young children.¹ PIV causes >30% of all acute respiratory infections in infants and children and is second only to respiratory syncytial virus (RSV) as a cause of lower respiratory tract infection (LRTI) in young children.² Outbreaks of PIV type 3 (PIV3) infection occur annually, mainly in the spring and summer, and PIV3 is more severe than other types of PIV, especially in infants.¹ Nevertheless, PIV3 outbreak in a neonatal intensive care unit (NICU) is less frequently reported than RSV. We experienced an outbreak of PIV3 in three infants in the NICU at Iwaki Kyoritsu Hospital. One infant with severe chronic lung disease (CLD) also had recurrent wheezing. This report will be valuable because it is the first to describe severe CLD in infants complicated with recurrent wheezing after PIV3 outbreak in the NICU.

Case reports

Patient demographics and clinical presentation are given in Table 1.

Case 1

The index patient was a 114-day-old female infant from a set of fraternal twins (with dichorionic diamniotic placenta on histopathology). She had been delivered at 28 weeks of gestation via emergency cesarean section due to chorioamnionitis. Birthweight was 974 g and Apgar scores was 6 and 7 at 1 and

5 min, respectively. Shortly after birth, she was intubated and ventilated for respiratory distress syndrome (RDS); she remained on a ventilator for 37 days from birth and required nasal continuous positive airway pressure (NCPAP) until day 75. She was diagnosed with CLD at 36 weeks' post-menstrual age (PMA). She did not require oxygen after being taken off NCPAP and developed wheezing. Apnea, fever, and cough were seen on day 114 (July 24). PIV3 was detected on virus culture, and pulmonary infiltrates were seen on chest radiography. The patient also required NCPAP or oxygen for another 13 days. The duration of respiratory symptoms was 17 days. She was discharged on day 136. The patient had recurrent wheezing after discharge, which reappeared with the common cold until 1 year of age.

Case 2

Patient 2 was a 115-day-old male infant, the sibling of patient 1. He had also been delivered at 28 weeks of gestation. His birthweight was 970 g and his Apgar score was 6 and 7 at 1 and 5 min, respectively. Shortly after birth, he was intubated and ventilated for RDS; he remained on a ventilator for 8 days and required NCPAP until day 71. He was diagnosed with CLD at 36 weeks' PMA. He developed apnea and cough on day 115, on July 25, 1 day after patient 1. PIV3 was detected on virus culture, but chest radiograph was unchanged. He did not require respiratory support such as NCPAP or oxygen. The duration of the respiratory symptoms was 7 days. He was discharged on day 136. He had no complications such as recurrent wheezing after discharge.

Case 3

Patient 3 was a 40-day-old male infant. He had been delivered at 35 weeks of gestation via emergency cesarean section

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Received 12 October 2016; revised 31 January 2017; accepted 4 August 2017.

Table 1 Patient demographics and clinical presentation

Patient ID no.	Birthweight (g)	GA (weeks)	CLD	Age at onset (days)	Clinical features	Investigations	Treatment	Duration of symptoms (days)	Recurrent wheeze
1	974	28	+	114	Apnea, fever, cough, wheeze	PIV3 culture	Nasal CPAP for 2 days Oxygen for 10 days	17	+
2	970	28	+	115	Apnea, cough	PIV3 culture	–	7	–
3	2,440	35	–	40	Cough, wheeze	PIV3 culture	–	6	–

CLD, chronic lung disease; CPAP, continuous positive airway pressure; GA, gestational age; PIV3, parainfluenza virus type 3.

because of total placenta previa bleeding. Birthweight was 2,440 g, and Apgar score was 7 and 8 at 1 and 5 min, respectively. After birth, he was intubated and ventilated for RDS for 2 days. He was not diagnosed with CLD at 36 weeks' PMA. He developed a cough on day 40, on July 29, 5 days after patient 1. PIV3 was detected on virus culture, but chest radiograph was unchanged. He did not require respiratory support such as NCPAP or oxygen. The duration of respiratory symptoms was 6 days. He had complications of wheezing, but the symptoms were self-limited. He was discharged on day 70. He did not have recurrent wheezing after discharge.

Outbreak

Between July and August 2013, an outbreak of PIV3 occurred in three infants in the present facility. Subsequently, no staff or visitor had clinical symptoms. On July 24, four infants were housed in the NICU and six in the growing care unit. After the index case, all symptomatic infants (patients 1–3) were screened for the viral antigen using pharyngeal swabs. In the outbreak setting, we reinforced standard infection control procedures, including handwashing; use of gowns, gloves, and masks; and cohort placement on July 25, 1 day after patient 1 developed symptoms. On July 31, after establishing a night nurse shift system, specific nurses cared for patients in the isolation room. We transferred the symptomatic infants (patients 1–3) to the isolation room to isolate them from asymptomatic infants, thereby preventing the spread of the virus.

Detection of PIV3

Symptomatic infants (patients 1–3) were screened using nasopharyngeal swabs and kits for rapidly testing for RSV, adenovirus, and influenza virus. They were also screened on virus culture for the viral antigen using pharyngeal swabs. All viral antigen tests were negative. PIV3 was isolated and identified in patients 1–3. PIV3 was isolated using African green monkey kidney (Vero) cells and identified using indirect immunofluorescence (Anti-Parainfluenza 3 Blend Antibody, clones 240/12D, 260/10B, MAB855-3; Merck Millipore, Darmstadt, Germany; and Polyclonal Rabbit Anti-Mouse Immunoglobulins/FITC, FITC, Immunofluorescence, F0232; Agilent Technologies, Santa Clara, CA, USA).

Discussion

Human parainfluenza virus type 3 outbreak in NICU is rare despite the prevalence of common pathogens in pediatric LRTI. Conversely, RSV is the most common pathogen of pediatric LRTI; consequently, RSV outbreaks in the NICU are more common than PIV3. These differences might be associated with the method and kit for rapid testing for the virus antigen. There is no method and kit for rapidly testing for PIV3; therefore, detection of PIV3 might be more difficult. In previous reports of PIV3 outbreak in NICU,^{2–8} virus culture and polymerase chain reaction (PCR) were used. PCR is a sensitive and rapid method for detecting virus, but they cannot always be performed at all facilities. Therefore, we chose virus culture for testing respiratory infections of unknown origin and detected PIV3. PCR for multiple respiratory viruses has been widely implemented, and its application is increasing because of the better sensitivity and rapid turnaround time in the clinical care setting. In addition, it is easier to simultaneously diagnose multiple viruses in patients with co-infection. The more we perform PCR for multiple respiratory viruses and virus culture for respiratory infections of unknown origin in the NICU, the more frequently we might detect respiratory viruses, such as PIV, rhinovirus, coronavirus, Coxsackie virus, and echovirus.

Most PIV infections are self-limited, but mortality and severe outbreaks in NICU that require ventilation have been reported in infants with severe comorbidities,^{2–8} but no case of recurrent wheezing after discharge has been reported (Table 2). Particularly, in the present patients, the index case of CLD was the most severe. The index patient, ventilated for a long time with CLD, required supportive treatment after PIV3 infection and had recurrent wheezing after discharge for a long time. RSV has frequently been associated with recurrent wheezing in preterm infants.¹ In terms of PIV, Welliver *et al.* reported a rate of 85% and of 10% for recurrent wheezing episodes following PIV bronchiolitis and upper respiratory tract infection, respectively,⁹ and LRTI may predispose to episodes of broncho-constriction on subsequent exposure. RSV and PIV have many structural, pathogenic, epidemiologic, and clinical similarities.¹ Therefore, the clinical course of PIV might be similar to that of RSV in many aspects. Preterm infants with bronchopulmonary dysplasia present with chronic

Table 2 Parainfluenza virus type 3 outbreak in neonates: Published reports

No. patients	Birthweight (g)	GA (weeks)	BPD	Age at onset	Clinical features	Treatment	No. deaths	Reference
7	UNK	UNK	UNK	UNK	Rhinitis, cough, poor feeding, irritability, rales, apnea, infiltrates, increased Oxygen requirement, cyanosis, lethargy	UNK	0	Meissner <i>et al.</i> (1984) ²
6	UNK	UNK	UNK	49–221 days	Rhinitis and increased secretions, tachypnea, wheezing, cyanosis and respiratory failure, pneumonia	Ventilation	0	Singh-Naz <i>et al.</i> (1990) ³
6	2,131	35	UNK	12 days	Nasal congestion, tachypnea, cough, desaturation	UNK	0	Moisiuk <i>et al.</i> (1998) ⁴
5	UNK	32	UNK	3 weeks	Stiffness, cough	UNK	0	Ng <i>et al.</i> (1999) ⁵
	UNK	UNK	UNK	UNK	UNK	UNK		
	1,070	32	+	66 days	Apnea, bradycardia, tachypnea, retractions	Nasal CPAP, Oxygen		
3	1,100	28	+	180 days	Coryza, cough, bronchiolitis	Nasal CPAP, Oxygen	2	Simmonds <i>et al.</i> (2009) ⁶
	860	29	+	141 days	Coryza, cough, tachycardia, bronchiolitis	Oxygen		
	2,080	32	–	16 days	Apnea, bradycardia, retractions	Nasal CPAP		
7	1,550	32	–	26 days	Apnea	Nasal CPAP, Oxygen	0	Teo <i>et al.</i> (2010) ⁷
	UNK	28	UNK	5 months	Cough, nasal congestion, wheezing	Ventilation		
6	UNK	30	UNK	6 weeks	Wheezing	Escalating ventilation	0	Ben-Shimol <i>et al.</i> (2013) ⁸
	UNK	33	UNK	17 days	URTI symptoms, apnea	Intubation		
	740	25	+	250 days	Retractions, tachypnea, cough, desaturations	Nasal CPAP, Oxygen		
	790	24	+	102 days	Cough, desaturations	Oxygen		
	960	34	+	84 days	Coryza, cough, apnea, tachypnea, retractions	Nasal CPAP, Oxygen		
	970	27	–	59 days	Apnea, bradycardia, cough, increased secretions	Nasal CPAP, ventilation		
	1,610	31	–	28 days	Apnea, bradycardia, coryza, nasal congestion, cough	Nasal CPAP		
	2,585	35	–	35 days	Coryza, nasal congestion, cough	None		
3	1,940	26	–	99 days	Sneezing, cough	None	0	Present study
	960	26	+	76 days	Desaturations	Oxygen		
	1,258	28	UNK	64 days	Desaturations	Oxygen		
	730	26	UNK	91 days	Rhinorrhea, dyspnea	None		
	900	26	UNK	88 days	Desaturations, rhinorrhea	Oxygen		
	1,004	27	UNK	54 days	Desaturations, rhinorrhea	Oxygen		
	1,016	27	UNK	63 days	Rhinorrhea, difficulty in oral feeding	None		
3	974	28	+	114 days	Apnea, fever, cough, (recurrent) wheeze	Nasal CPAP, Oxygen	0	Present study
	970	28	+	115 days	Apnea, cough	None		
	2,440	35	–	40 days	Cough, wheeze	None		

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; GA, gestational age; UNK, unknown; URTI, upper respiratory tract infection.

airway obstruction defined as recurrent episodes of wheezing and decreased lung function tests; and in some of these infants, obstructive lung disease persists into adulthood.¹⁰ We speculate that the index case of severe CLD and PIV3 infection in a preterm infant early after birth worsened lung function, prompting the requirement for NCPAP. PIV3 infection might cause recurrent wheezing as observed in RSV infection, but it is not clear whether the present case of recurrent

wheezing was caused by this PIV3 infection alone. We should consider PIV3 as one of the pathogens of respiratory infection of unknown origin in the NICU, and provide attention to severity if preterm infants with CLD develop PIV3 infection.

Disclosure

The authors declare no conflict of interest.

Author contributions

H.M. drafted the manuscript; K.H. reviewed the manuscript; Y.H. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

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