

Parainfluenza Type 3 Viral Outbreak in a Neonatal Nursery

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Abstract

An outbreak of parainfluenza virus type 3 infection that occurred in a special neonatal care unit is described. Birth weights of affected infants ranged from 1860 to 2080 g and gestational ages were between 28 and 32 weeks. Three infants presented with recurrent episodes of apnoea associated with oxygen desaturations on postnatal ages of 16 days, 26 days and 66 days respectively; upper respiratory tract infection symptoms such as coryza were absent in them. Two older infants who had oxygen dependent bronchopulmonary dysplasia presented with worsening of the respiratory status due to bronchiolitis at 5 and 6 months of age respectively. All infants required supplemental oxygen and assisted ventilatory support and there were no deaths. Parainfluenza virus type 3 was identified by direct antigen detection in 3 cases and was isolated in the other two. The outbreak was controlled by isolating the infected infants, use of gowns and strict hand washing. Nonporous surfaces contaminated with parainfluenza virus type 3 were cleansed with water and detergent. Viral respiratory infections should be considered in the differential diagnosis when growing premature infants present with recurrent apnoeic episodes and they may be severe enough to require assisted ventilatory support. The source of the outbreak was possibly a medical officer and a medical student who had an upper respiratory tract infection prior to the outbreak in the nursery. Medical and nursing staff with viral respiratory infections should avoid working in the nurseries until they are well.

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Introduction

Parainfluenza viruses are relatively large RNA paramyxoviruses. Four serologic types cause disease in humans. Parainfluenza type 3 virus closely mimics, respiratory syncytial virus in its clinical manifestations and in infants, it is the second commonest cause of pneumonia and bronchiolitis after respiratory syncytial virus.¹⁻³ It is also an important cause of croup and bronchitis in older children.^{4,5} Rarely, infection of other organs including the central nervous system, has been demonstrated.⁶

Parainfluenza type 3 virus (PIV-3) is an important nosocomial pathogen.⁷⁻⁹ In December 1994 we observed an outbreak of nosocomial respiratory infection with parainfluenza type 3 virus in the special care neonatal unit of the Kandang Kerbau Hospital. The characteristics of this outbreak are described.

Materials and Methods

Patients

The case records of all infants in the special care nursery who were affected during the outbreak were reviewed for pertinent data related to their illness, including dates and onset of symptoms, spectrum of clinical features, feeding history, clinical status prior to illness, chest X-ray findings, details of treatment including respiratory support and duration of the illness. The birth weight, gestational age, apgar scores, neonatal problems and dates of admission to the nursery were also noted.

There were 5 premature infants who were affected in the outbreak, three of whom who had bronchopulmonary dysplasia (BPD) were of postnatal ages 2, 5 and 6 months, respectively. The index case (case 1) presented on 29 December 1994 and two cases (cases 2 and 3) presented a few hours later. The final two nosocomial

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cases presented the following day.

Laboratory Studies

For infants who were unwell the investigations included full blood count, C-reactive protein, chest radiograph, blood culture and spinal fluid culture. A viral origin as the cause of the outbreak was sought for when two of the babies were noted to have coryza. Nasopharyngeal aspirates were collected in saline in mucus traps for direct respiratory virus antigen detection at the Virus Laboratory of the Department of Pathology, Singapore General Hospital. The aspirated secretions were sent in Hanks' virus transport medium on ice to the laboratory as soon as possible for culture of the respiratory viruses.

Direct Antigen Detection By Immunofluorescence Assay

The immunofluorescence assay (IFA) was carried out by centrifuging cells down from the mucus and suspension medium in nasopharyngeal aspirates. The cells were deposited onto wells of teflon-coated slides, fixed and each well stained individually with mouse monoclonal antibodies to respiratory syncytial virus, adenovirus, influenza A and influenza B and pooled monoclonal antibodies to parainfluenza types 1-3 (World Health Organization Influenza Collaborating Center, Centers for Disease Control, USA). The stained cells were then reacted with fluorescein-conjugated rabbit anti-mouse immunoglobulin (Dako, Dako A/S, Denmark) and the slides read with a fluorescence microscope. Infected cells fluoresced apple-green with the appropriate antiserum. When parainfluenza virus was detected, a second IFA was performed on spare wells using separate monoclonal antibodies to parainfluenza 1, parainfluenza 2 and parainfluenza 3 directly conjugated to fluorescein (Imagen, Dako Diagnostics Ltd, UK) to type the virus.

Virus Isolation

Where virus isolation was requested, the specimen was inoculated into tubes of HeLa, human embryo fibroblasts, LLC-MK2 and Mardin-Darby canine kidney (MDCK) cells, as well as MDCK shell-vial cultures. The tubes were incubated at 33°C and examined daily for cytopathic effects (CPE) for up to 21 days, after which they were discarded. One tube each of the inoculated LLC-MK2 and MDCK cells were tested on day 5 and day 10 post-inoculation, or earlier if CPE was evident, for parainfluenza and influenza viruses by immunofluorescence assay (IFA) (vide supra). Shell-vial cultures were screened on day 5 for influenza virus by haemagglutination and if positive, typing of the virus was carried out by IFA and haemagglutination inhibition. Cells for the IFA were obtained by scraping them off the culture tubes or by centrifuging the culture medium from shell-vial cultures.

Statistical Analysis

Independent Student's t-test was used to assess gestational age at birth and birth weight as a predisposing factor for symptomatic PIV-3 infection. Statistical significance was defined as $P < 0.05$.

Results

There were 5 affected infants. The gestational ages of the infants ranged between 28 to 32 weeks and their birth weights were between 860g and 2680g. Symptoms began abruptly and the manifestations included coryza (2), cough (2), recurrent apnoeic spells (3), chest retractions (2), episodes of bradycardia (2), sinus tachycardia (1) and tachypnoea (1). Duration of the illness ranged from 2 to 17 days with a mean of 7 days. The characteristics of the infants involved in the outbreak are shown in Table I. Of the 5 affected infants, PIV-3 antigen was detected directly in cells from the nasopharyngeal aspirates of 3 babies and the virus was isolated from those of the other two. All babies required management in the neonatal intensive care unit where the duration of stay ranged from 2 to 13 days, with a mean of 6 days. All 5 infants required continuous positive airway pressure of 4 to 5 cmH₂O which was given using Hudson prongs (nasal CPAP). The 2 older infants with BPD also required bronchodilators at four hourly intervals. Three infants were started on intravenous antibiotics; this was stopped when co-infections with other bacteria or viruses were excluded.

There were 21 babies at risk during the outbreak, giving an attack rate of 23%. The median gestational age at birth between symptomatic infants was 32 weeks compared with a median age of 36.5 weeks for well infants ($P = 0.015$, CI: -8.3 to -1.0). Median birth weight for symptomatic and well infants was 1100 g and 2437 g, respectively ($P = 0.005$, CI: -1841.0 to -381.2). Three out of 4 infants with underlying BPD were symptomatic.

Control of the outbreak was achieved through isolation of the infected babies, use of gowns and strict handwashing before and after handling the infants. Nonporous surfaces contaminated with PIV-3 were cleansed with water and detergent. There were no deaths. We speculate that the source of the outbreak was possibly a medical officer and a medical student who had an upper respiratory tract infection prior to the outbreak in the nursery.

Discussion

The contagiousness of respiratory viruses has been well documented in the literature. However, the relatively smaller number of reported viral outbreaks as compared to those caused by bacteria probably reflects a lack of clinical recognition rather than infrequency of occurrence. Nosocomial nursery outbreaks due to sev-

TABLE 1: CHARACTERISTICS OF PREMATURE BABIES INVOLVED IN THE OUTBREAK

Case	Birth weights/ Gestational age	Age of onset	Clinical features	Investigations	Treatment	Duration of symptoms
1	1070 g 32 wks	66 days	Recurrent apnoea Bradycardia Tachypnoea Retractions	PIV-3 antigen +ve	Patient originally on hood oxygen for BPD, required nasal CPAP support for 2 days → hoodoxygen	3 days
2	1100 g 28 wks	180 days	Coryza Cough Prolonged expiration Rhonchi Crepitations Bronchiolitis	PIV-3 antigen +ve	Patient originally on hood oxygen for BPD, required nasal CPAP support for 12 days → hood oxygen Bronchodilators	17 days
3	860 g 29 wks	141 days	Coryza Cough Tachycardia Prolonged expiration Crepitations Bronchiolitis	PIV-3 culture +ve	Patient already on nasal CPAP for BPD → hood oxygen (after 7 days) Bronchodilators	11 days
4	2080 g 32 wks	16 days	Recurrent apnoea Bradycardia Retractions	PIV-3 culture +ve	Nasal CPAP for 3 days	3 days
5	1550 g 32 wks	26 days	Recurrent apnoea	PIV-3 antigen +ve	Nasal CPAP for 2 days → hood oxygen for 1 day	3 days

BPD: bronchopulmonary dysplasia; CPAP: continuous positive airway pressure; PIV-3: parainfluenza type 3 virus

eral respiratory viruses such as respiratory syncytial virus (RSV), influenza, parainfluenza, rhinovirus and adenovirus,^{7,10-15} enteroviruses such as coxsackie, echovirus^{16,17} and rotaviruses have been described. PIV-3 causes endemic outbreaks,^{2,5,18} with occasional low grade epidemicity.^{1,3} PIV-3 respiratory infections are associated with significant morbidity and nosocomial outbreaks in neonatal nurseries and paediatric wards have been reported.

In the PIV-3 outbreak reported by Karron et al,⁸ 6 of the 17 children were less than 6 months of age, and apnoea, bradycardia and changes in oxygen requirement were significantly more common in them as compared against children more than 6 months of age. In their study, 1 apnoeic infant required assisted ventilation, whereas in the present study, all cases required assisted ventilation. This would stress the fact that young infants, particularly premature infants with viral respiratory illness, should be closely monitored with pulse oximetry and cardio-respiratory monitors.

Moscovici et al⁹ in January 1960 identified PIV-3 as the cause of an outbreak of respiratory illness involving 27 premature babies. PIV-3 was isolated in 8 of the 27 premature babies. Most of the newborns presented with stuffy nose and mucoid nasal discharge, half of them developed pneumonia, which resulted in one death. The disease in older children was characterised by sudden onset of low grade fever and a dry hacking cough;

several had bronchiolitis. The majority of them had a low to normal white blood cell count with a predominance of lymphocytes.

As exemplified in the present study, the patterns of infection caused by PIV-3 in newborn babies may be quite different from those observed in older children. The presenting manifestations in premature infants are often atypical and they include recurrent apnoeic episodes, sepsis-like syndrome and unexplained worsening of BPD usually with increasing supplemental oxygen requirements and recurrent wheezing. Often these infants are sick and require assisted ventilation. Neonates are obligatory nasal breathers and have the potential of developing severe illness with blocked nasal passages and this would explain why some of the neonates in this study developed apnoea and needed assisted ventilation. Moreover, recurrent apnoeic spells may be the only manifestation of a lower respiratory tract infection, particularly in preterm infants. PIV-3 infections may prolong the duration of hospitalisation of premature infants and also the duration of oxygen requirement in infants with BPD. Other respiratory viruses such as RSV, influenza, rhinovirus and adenovirus can also present with similar manifestations. Rarely PIV-3 can invade other organs other than the respiratory system. Meningitis, meningoencephalitis and disseminated disease have been reported in young infants.^{6,19} Guillain-Barre syndrome and demyelination syndrome associated with

PIV-3 have been described in adults who are either immunocompetent or immunocompromised.²⁰⁻²²

It should also be noted that in the presence of a nursery outbreak of respiratory tract disease, more than one virus may circulate concurrently. Concurrent outbreaks of RSV and PIV-3⁷ as well as rhinovirus and RSV¹⁰ in newborn nurseries have been described; thus an individual infant may be infected simultaneously by more than one virus. Multiple strains of PIV-3 have been reported during a single epidemic. Reverse transcription polymerase chain reaction (RT-PCR) amplification and sequencing of the hypervariable 5' non coding region of the F gene of PIV-3 has been used to distinguish between nosocomial transmission and community acquired infection during an outbreak.⁸

Transmission of parainfluenza viruses has been less well studied. At the present time it is thought that both direct person-to-person contact and inhalation of infectious droplets are important routes of spread.^{7,22} Both routes may have been important in the above outbreak. Parainfluenza viruses have been found to survive for at least a few hours in air and on environmental surfaces.^{23,24} Infectious viruses can be transferred from environmental surfaces to the hands of hospital personnel who appear to be important for their spread.²⁵

The general measures for control of an epidemic of PIV-3 include detailed epidemiologic investigation. Control measures such as proper and regular handwashing, isolation of the infected patients, cohorting of infected and susceptible patients and disinfection of hard environmental surfaces are associated with decreased spread of this virus.²⁵ Hard non-porous surfaces contaminated with PIV-3 can easily be disinfected with a variety of commercial and noncommercial formulations. The hospital infection control committee has an active role in the development and ongoing review of the relevant employee health programmes. Health care workers must be educated concerning the possible risks of transmission or acquisition of respiratory viruses to or from the infants in the nursery. Infection control programmes must 'address the issue of work restriction for personnel with viral respiratory illnesses and formulate rational, workable guidelines suitable to the institution. In view of the fact that premature neonates and infants with BPD are vulnerable to complications of influenza and cannot be protected by influenza vaccination, annual influenza immunization of nursery personnel has been strongly recommended.^{26,27} On the contrary, influenza and parainfluenza nosocomial infections are relatively uncommon in the paediatric setting compared to other viruses,²⁸ the most common being rotavirus, adenovirus, rhinovirus and RSV and hence the usefulness of influenza vaccination in the nursery setting is debatable unless there is an epidemic. Significant progress has been made in recent years towards the

development of candidate vaccines against PIV-3 infections²⁹, their role regarding immunization of nursery personnel, infants with BPD and prevention of outbreaks among premature neonates in the nursery needs to be studied.

In summary, as seen in this study, outbreaks of PIV-3 can be associated with significant morbidity in premature infants. Viral respiratory infections should be considered in the differential diagnosis in growing premature infants presenting with recurrent apnoeic spells, sepsis-like syndrome or worsening of underlying bronchopulmonary dysplasia and necessary control measures should be instituted promptly in order to decrease the nosocomial spread of the viruses to other infants in the nursery.

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