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Original Article

Hospitalized Pediatric Parainfluenza Virus Infections in a Medical Center

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BACKGROUND/PURPOSE: Parainfluenza viruses (PIVs) are common pathogens in respiratory tract infections. The aims of this study were to determine the clinical presentation of PIV infections in hospitalized children and to identify particular clinical indications that may effectively distinguish between different PIV serotypes.

METHODS: A retrospective review of data from children hospitalized with PIV infections at the Mackay Memory Hospital in Taipei between January 2005 and December 2007 was undertaken. Symptoms, signs, laboratory findings and seasonal variations between different types of PIV (serotypes 1, 2 and 3) were compared.

RESULTS: A total of 206 patients [119 (57.8%) boys and 87 (42.2%) girls] were enrolled in the study. Seventy-four (35.9%) patients were infected with PIV serotype 1, 25 (12.1%) with serotype 2 and 107 (51.9%) with serotype 3. The most common clinical presentations were fever (81.1%), cough (66.0%), rhinorrhea (44.2%) and hoarseness (22.3%); 4.9% of the infected children also had skin rashes. No significant differences were found in average white blood cell counts and C-reactive protein levels between the three serotypes. PIV serotype 1 infections were discernible throughout the year; serotype 2 tended to cluster in the late summer and autumn of 2005 and 2007; and serotype 3 was more common in the spring and early summer.

CONCLUSION: The clinical presentation of PIV infection in hospitalized children ranges from upper respiratory tract infection to croup, bronchiolitis and viral bronchopneumonia, with the different types of PIV infections giving rise to similar symptoms. The seasonal distribution of the different serotypes is, nevertheless, quite distinct.

KEYWORDS: children, parainfluenza virus infections, respiratory infections

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Introduction

Parainfluenza virus (PIV) and respiratory syncytial virus (RSV) belong to the genus *Paramyxoviridae*. These PIVs are enveloped RNA viruses and commonly cause lower viral respiratory tract illnesses in children and high-risk populations.[1,2] They are also a major cause of the hospitalization of children, with infants and younger children in particular being the major target for such infections.[3–7] Four types of PIV infection have been identified since 1960.[8,9] PIV-related mortality and complications are typically reported in immunocompromised patients.[1,4,8–11] Such infections may be asymptomatic in older children and adults, or they may even mimic a common cold. Reinfection by PIVs is common throughout the life because they often lack any durable immunity after a natural infection.[1,6] The primary aims of this study were to determine the clinical manifestations of PIV infections in hospitalized children, and to uncover clues that might help to establish clinical distinctions between different PIV serotypes.

Methods

Patients and data collection

We reviewed the charts of pediatric patients from whom PIVs had been isolated as a result of throat cultures, and who were subsequently hospitalized at the Mackay Memorial Hospital in Taipei between January 2005 and December 2007. Cell lines, including Hep-2, MCDK, MRC-5 and A459 were used as the routine viral survey for respiratory tract infections. In those cases where a cytopathic effect was detected by microscopy, we used a specific monoclonal antibody from a commercially available respiratory viral panel[1] (for herpes simplex virus, influenza A & B, parainfluenza 1–3 and adenovirus) and an identification kit (Light Diagnostic, Chemicon International Inc, Temecula, USA) to identify the virus-infected cells. Three serotypes of PIV were identified.

We recorded the clinical manifestations and diagnoses for each of the patients. Acute rhinitis, acute pharyngitis or tonsillitis were defined as the upper respiratory tract infection (URTI) group, while the lower respiratory tract infection (LRTI) group included patients with acute bronchiolitis, bronchopneumonia and pneumonia. Patients diagnosed with croup were allocated to a separate group. Respiratory tract symptoms or fever developing more than 7 days after hospitalization were defined as nosocomial infections. Positive findings of a rotavirus antigen, mycoplasma serologic results or culture evidence suggesting other pathogens were all regarded as co-infections.

The clinical information for the sample patients in this study was obtained either from initial post-hospitalization laboratory data or from data recorded at the time of the nosocomial infections. A C-reactive protein (CRP) level higher than 0.8 mg/dL was defined as an abnormal elevation. During the analysis of the laboratory data, all data on patients with co-infection or malignancy were excluded from the study. Analysis and comparison of clinical presentations, laboratory data and seasonal variations in PIV infections for each of the three different serotypes were subsequently carried out.

Statistical analysis

The analysis of variance approach was used to examine the clinical presentations of the different PIV serotypes, with a comparison being undertaken between the categorical data using the χ^2 test or Fisher's exact test. A p value of < 0.05 was considered to be statistically significant.

Results

Patient distribution

The throat cultures of 218 pediatric patients yielded positive PIV samples during the study period. Following the exclusion of all data pertaining to outpatients, 206 inpatients were enrolled in the study. Of these, 119 (57.8%) were boys and 87 (42.2%) were girls (male to female ratio = 1.37:1).

There were 74 (35.9%) cases of PIV serotype-1 infection (PIV-1), 25 (12.1%) cases of PIV serotype-2 infection (PIV-2), and 107 (51.9%) cases of PIV serotype-3 infection (PIV-3). Approximately two-thirds (134; 65.0%) of the children were under the age of 3 years while 57 (27.7%) were less than 1 year old. Only 12 (5.8%) were over the age of 5 years.

The mean age of all PIV-infected children was 25.0 ± 14.3 months. The mean age of the PIV-1-infected group was 28.5 ± 19.4 months, while that of the PIV-2-infected group was 30.9 ± 18.8 months, and that of the PIV-3-infected group was 21.7 ± 11.7 months. Those children with PIV-3 infections were significantly younger than those with PIV-1 infections ($p = 0.022$). Furthermore, there

Table 1. Clinical presentation of different serotypes of parainfluenza virus infections[a]

Clinical presentation	Total (n=206)	PIV-1 (n=74)	PIV-2 (n=25)	PIV-3 (n=107)
Fever	167 (81.1)	64 (86.5)	18 (72.0)	85 (79.4)
Cough	136 (66.0)	48 (64.9)	20 (80.0)	68 (63.6)
Rhinorrhea	91 (44.2)	29 (39.2)	13 (52.0)	49 (45.8)
Hoarseness[b]	46 (22.3)	22 (29.7)	7 (28.0)	17 (15.9)
Tachypnea	39 (18.9)	15 (20.3)	5 (20.0)	19 (17.8)
Wheezing[c]	19 (9.2)	4 (5.4)	5 (20.0)	10 (9.3)
Nasal obstruction	9 (4.4)	3 (4.1)	2 (8.0)	4 (3.7)
Tonsil with exudate	6 (2.9)	3 (4.1)	1 (4.0)	2 (1.9)
Diarrhea	23 (11.2)	6 (8.2)	2 (8.0)	15 (14.0)
Vomiting	21 (10.2)	8 (10.8)	2 (8.0)	11 (10.3)
Skin rash	10 (4.9)	1 (1.4)	2 (8.0)	7 (6.5)

[a]Data presented as n (%); [b]significantly more episodes of hoarseness were caused by PIV-1 infections than by PIV-3 infections (p=0.026, χ^2 test); [c]significantly more episodes of wheezing were caused by PIV-2 infections than by PIV-1 infections (p=0.028, χ^2 test). PIV=parainfluenza virus.

Table 2. Respiratory tract diseases in different types of parainfluenza virus[a]

Respiratory symptom	Total (n=206)	PIV-1 (n=74)	PIV-2 (n=25)	PIV-3 (n=107)
None	24 (11.6)	9 (12.2)	1 (4.0)	14 (13.1)
URTI	61 (29.6)	19 (25.6)	7 (28.0)	35 (32.7)
Croup[b]	45 (21.8)	22 (29.7)	6 (24.0)	17 (15.9)
LRTI	76 (36.9)	24 (32.4)	11 (44.0)	41 (38.9)

[a]Data presented as n (%); [b]significantly more episodes of croup were caused by PIV-1 infections than by PIV-3 infections (p=0.027, χ^2 test). PIV=parainfluenza virus; URTI=upper respiratory tract infection; LRTI=lower respiratory tract infection.

were no apparent cases of a child having a PIV re-infection, even with a different serotype.

Clinical presentation

As shown in Table 1, the most common clinical presentations were fever (81.1%), cough (66.0%), rhinorrhea (44.2%), hoarseness (22.3%), tachypnea (18.9%) and wheezing (9.2%). Comparison of the clinical manifestations between the three PIV serotypes revealed that PIV-2 caused more frequent episodes of wheezing than PIV-3 (p=0.028).

Cases presenting with hoarseness were also more frequent in children with PIV-1 than in those with PIV-3 infection (p=0.026). The PIV-infected children examined in this study also presented with gastrointestinal tract symptoms, including vomiting (10.2%) or diarrhea (11.2%), but only a few patients had maculopapular skin rashes (4.9%). Most PIVs caused obvious respiratory tract infections and, indeed, only a very small proportion (11.6%) of children presented with no respiratory symptoms (Table 2).

Both URTI and LRTI were caused by different serotypes of PIV and the ratios were quite similar. However, the proportion of croup cases was higher with PIV-1 infection than with PIV-3 infection (p=0.026) (Table 2). A total of 14 children (6.8%) were diagnosed with nosocomial PIV infections; 13 (6.3%) had congenital anomalies (including Down's syndrome, Pierre-Robin syndrome and chromosome anomalies) and a further 14 (6.8%) were recorded as pre-term deliveries. Concomitant diseases, such as gastroenteritis, acute otitis media, pyuria, urinary tract infection, sepsis or soft tissue infection were found in 84 (40.6%) of the children examined in this study.

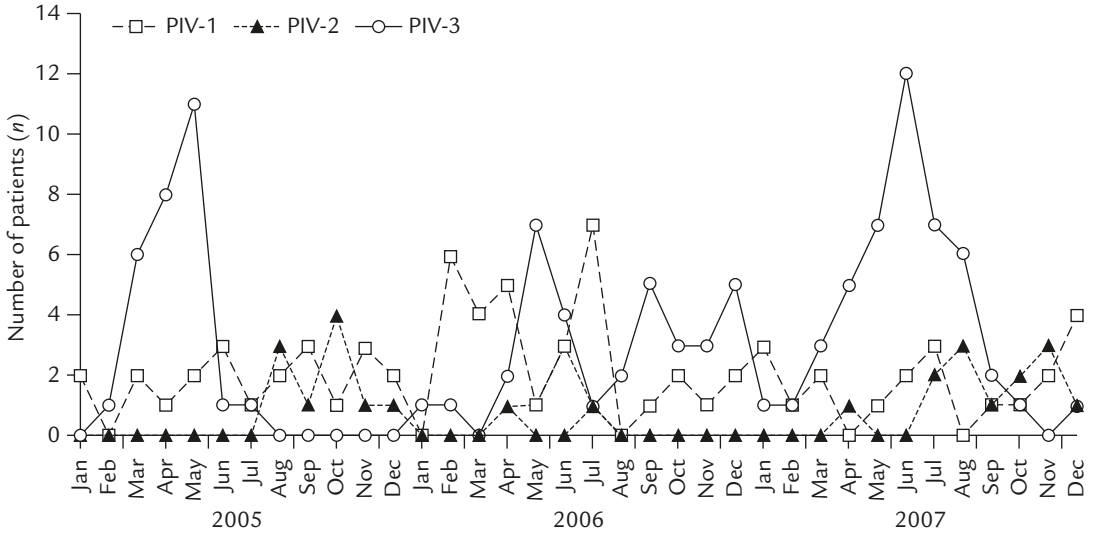

Figure. Number of patients with different serotypes of parainfluenza virus infections, 2005–2007. PIV=parainfluenza virus.

Our results also show that 30 of the children (14.6%) had culture- or serology-proven co-infections, such as RSV, rotavirus, enterovirus, adenovirus, methicillin-resistant *Staphylococcus aureus, Escherichia coli, Salmonella*, *Enterobacter species* and *Mycoplasma pneumoniae*. No statistical differences were discernible between the three types of PIV infections with regard to the duration of symptoms/signs prior to hospitalization (3.2±2.6 days), the duration of fever (4.0±2.2 days) or the length of hospital stay (5.6±2.9 days).

Laboratory results

Laboratory data on one acute leukemia patient with pancytopenia and data on other patients who presented with co-infections were excluded from the total study sample of 206 patients. The hemoglobin levels of 175 of the sample patients ranged between 6.9–15.6 g/dL while the white blood cell counts ranged between 2.3–30.1 $\times 10^9$/L, with a mean of 10.4 $\times 10^9$/L.

The platelet count in 172 of the sample patients ranged between 137.0–731.0 $\times 10^9$/L. CRP levels, which were available for only 160 patients, ranged between 0.02–19.9 mg/dL, with elevated CRP levels (>0.8 g/dL) being evident in 39% of patients. No statistically significant differences were found in the laboratory results between patients with different PIV serotypes.

Seasonal variation

Evidence of PIV infections was found throughout the year during the study period (2005–2007), with PIV-1 infections commonly occurring throughout the entire period, and no seasonal peak being discernible. There were relatively fewer cases of PIV-2 infection, but there were two clear episodes of clustering in the summer/autumn of 2005 and 2007. PIV-3 infections were the most common, with clustering being evident in northern Taiwan in the spring and early summer periods (Figure).

Discussion

PIV infections are generally associated with various upper and lower respiratory tract diseases, despite the fact that some of the children in this study presented no signs whatsoever of respiratory tract infection. Indeed, it has been reported that, of all PIV-infected infants or children, only 25% will generally develop clinically significant PIV diseases.[3] Since most of the hospitalized children examined in this study (95%) were under 5 years of age, it may well be that younger children (with relatively immature immune systems) may present with much more severe illnesses after becoming infected with PIV and would therefore have a greater demand for hospital care. Although cases of re-infection with PIV have been reported in the early stages of childhood,[1,5] no such cases were evident in the present study.

Like RSV, PIV can cause respiratory symptoms/signs including fever, cough, massive nasal secretion, tachypnea and wheezing; however, compared with data on RSV, there are relatively few results relating to PIV-hospitalized

children.[1,12,13] According to previous studies, more severe respiratory illnesses are caused by PIV-3 than by serotypes 1 and 2.[1,5–6,8,11,12] However, in the present study, we found that the three PIV serotypes caused similar levels of URTI and LRTI. The reason for this may be that only hospitalized patients were enrolled in this study, so there may have been no significant differences in the severity of the illnesses.

Croup, one of the major reasons for hospitalization in infants and young children, is usually recognized as a typical clinical manifestation of PIV infections, particularly of type 1.[3,4,12] However, PIV-2 was reported to have caused over 60% of all croup cases in one community in years during which PIV-1 was not endemic.[1,9] Furthermore, a related study reported that PIV-1 accounted for all croup cases,[4] whereas in the present study, we determined that 51% of all croup cases were caused by PIV serotypes 2 or 3.

Other viruses, in addition to PIV, may also cause croup in children. These include RSV, influenza A and B, adenoviruses, rhinoviruses and *Mycoplasma*.[10] While influenza A infection is known to be more severe than PIV, it is nevertheless difficult to differentiate between the two based upon clinical symptoms alone.[4] In this study, we did not simultaneously isolate the influenza virus from PIV-infected children and, indeed, three children who had high fever and severe dyspnea were initially diagnosed with bacterial tracheitis.

PIV infections may also have extra-respiratory tract symptoms/signs. For example, 10% of the patients in the present study had gastrointestinal involvement, although skin rashes were less prevalent than in an earlier study.[4] PIV can cause many clinical diseases in adults, however, isolating viruses from the throats of adults is more difficult than from children, essentially because of the shorter incubation period and lower viral load shedding seen in adults.

PIVs, which have been isolated from immunocompromised patients with LRTI, are also a common cause of fever and neutropenia in children with cancer.[9] Viral load shedding has been shown to persist for a considerable length of time in immunocompromised patients (including those receiving bone marrow transplants or immunosuppressive agents) as well as those with leukemia, immunodeficiency and chronic disease.[1,9] Although severe morbidity and mortality rates relating to PIV infections are invariably associated with immunocompromised patients,[14–16] no mortality or severe sequelae occurred in any of the patients in the present study, despite the fact that some had underlying diseases.

Marx et al reported that PIV serotypes 1 and 3 infections occurred with distinct seasonal patterns, with such patterns found to be interactive amongst all three PIV serotypes.[17] While PIV-1 infections occur the whole year round, PIV-2 infections are relatively less regular and predictable, although clusters of the infection have been reported to have a biennial pattern.[1,4,8] In this study, we also found clustering in the late summer to autumn periods of 2005 and 2007, but not 2006, while clusters of PIV-3 infections occurred mainly in the spring and early summer. Similar epidemiological findings are reported in other studies,[6,18] although one study carried out in New York found that PIV infections tended to peak during the autumn months.[19] Finally, some respiratory tract viruses may interact with others. A report in Mexico showed that a PIV epidemic was also associated with RSV and influenza epidemics.[20]

This was a retrospective study and records may be incomplete, which may result in statistical bias. We performed throat viral cultures only on hospitalized patients or outpatients with severe infections. If we are to gain a complete understanding of the exact epidemiology of PIV infections, surveillance of both inpatients and outpatients are necessary.

Nevertheless, our data reveal the conditions for PIV infection in hospitalized children. In children, it is quite difficult to differentiate between one type of PIV infection and another, whether by clinical symptoms or by laboratory results. Although our analysis does not reveal any differences in the severity of the different PIV serotypes, it does reveal differences in their endemic seasons.

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