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Clinical manifestations of parainfluenza infection in children

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Parainfluenza viruses are major pathogens causing respiratory illness, manifesting from mild upper respiratory tract infection to bronchiolitis and pneumonia. This retrospective study aimed at providing clinical and epidemiologic data addressing the parainfluenza virus infection in Taiwan. A total of 39 patients were enrolled in this study from March 1999 to December 2000. Infants and young children were the major susceptible population, with 87.2% of them younger than 3 years. No seasonal trend was noted for parainfluenza type 1 and type 2 infections. One clustering of parainfluenza virus type 3 infections occurred in late spring of 2000 based on collected results. Parainfluenza type 1 viral isolates accounted for all of the cases of croup. Most isolates of parainfluenza virus type 3 were associated with upper and/or lower respiratory tract infections. A substantial proportion of the patients had skin involvement; the identification of one case of possible parainfluenza virus-related erythema multiforme is particularly interesting, especially because the chances of a causal relation between viral infection and skin symptoms are formerly thought to be slight. The identification of parainfluenza virus in illnesses classically considered to be due to other viruses is intriguing and may have important implications in the management of childhood illness clinically.

Key words: Children, croup, erythema multiforme, parainfluenza viruses

Parainfluenza viruses are important pathogens of human respiratory tract diseases in children. They are one of the most common causes of respiratory illness, manifesting from mild upper respiratory tract infection to bronchiolitis and pneumonia [1-3]. It has been estimated that parainfluenza viruses account for 40% of acute lower respiratory tract illnesses in children from which a virus is recoverable [4]. In adults, upper respiratory tract infections due to parainfluenza viruses are usually mild and self-limiting, rarely causing pneumonia [5]. However, in immunocompromised adults, parainfluenza virus infection may also cause disastrous cascades [6-11].

Five parainfluenza viruses isolated from humans among the flurry of new viruses had been identified in the late 1950s [12-14]. They are a group of spherical, enveloped, single-stranded RNA viruses in the *Paramyxoviridae* family [15] and types 1, 2, and 3 are the 3 major types causing human disease [4]. The seasonal patterns vary. Types 1 and 2 tend to occur as biennial epidemics in the summer and fall, while type 3 is endemic and occurs throughout the year [2,3,16]. Parainfluenza virus types 1 and 2 are thought to affect mostly pre-school-aged children [17] and their major clinical manifestations are croup, upper respiratory infection, and pharyngitis [2]. On the other hand, parainfluenza virus type 3 is mainly responsible for upper respiratory tract infection in all age group [2,3].

Although parainfluenza viruses have been well studied in previous medical literature, there has been little information addressing parainfluenza viral infection in Taiwan. This retrospective study tried to clarify the clinical manifestations of infections caused by parainfluenza virus in Taiwan.

Materials and Methods

In this retrospective study, all materials were obtained from chart records. All of the patients were suffering from infections of parainfluenza virus from March 1999 to December 2000 based on culture from throat swab and/or antigen detection of parainfluenza virus types 1 and 3 by direct fluorescence assay method. Rapid tests for parainfluenza serotypes 2 and 4 were not routinely available in National Taiwan University Hospital. Four patients infected by the parainfluenza type 3 were excluded from clinical analysis because no chart records were available. However, these four cases were included in Figure 1 for epidemiologic considerations.

Five cell lines were used for virus culture, including MDCK, HEL, HEP2, RB, and MK2. Hemadsorption test was also done in suspicious cytopathologic cell lines. In positive hemadsorption test cells, monoclonal antibody (DAKO Diagnostics Ltd., Cambridgeshire, UK) was further used to identify the different types of

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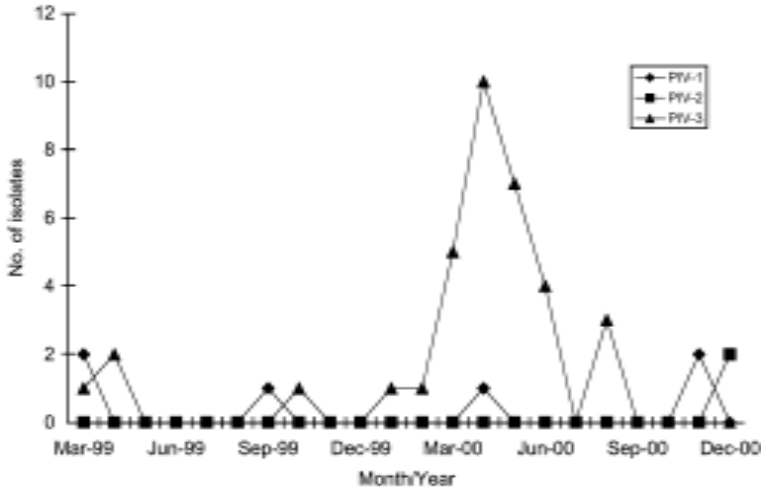

Fig. 1. Monthly distribution of parainfluenza infections from March 1999 to December 2000 (a total of 43 cases infected by parainfluenza virus were enrolled based on the positive virologic results).

parainfluenza viruses. Direct fluorescence assay (DAKO Diagnostics Ltd.) method was used for rapid antigen test in sputum specimens or nasopharyngeal suction specimens. All collected specimens were centrifuged at 12 000 rpm for 10 min. The sediments were smeared and fixed on fluorescence assay slide with acetone for 10 min. The monoclonal antibody (DAKO Diagnostics Ltd.) was then used to identify parainfluenza virus type 1 or type 3.

This study analyzed the clinical manifestations of these patients. Factors studied included age and sex distribution, clinical illness, clinical presentations, and laboratory tests.

Results

From March 1999 to December 2000, a total of 39 patients were identified according to positive virus isolation and/or positive sputum parainfluenza antigen detected by direct fluorescence assay method. Twenty-seven specimens were collected during their hospitalization. Six specimens were from the emergency department and the other 6 specimens were collected from the outpatient department. Among the 39 patients, 31 were infected by parainfluenza virus type 3 (30 patients were confirmed by throat virus isolation and 1 by both throat virus isolation and sputum antigen detection). Six patients were infected by parainfluenza virus type 1 from sputum antigen examination, and 2 isolates of parainfluenza virus type 2 were isolated from throat swab.

Age and sex distribution

There were 26 males and 13 females with a male to female ratio of 2:1. Their ages ranged from 12 days to 60 years. Most (87.2%) of them were younger than 3 year, 16 (41%) were younger than 1 year, 14 (35.9%) aged between 1 and 2 years, 4 (10.3%) aged between 2 and 3 years, 2 (5.1%) aged between 3 and 4 years, and the other 3 (7.7%) aged 13 years, 38 years, and 60 years, respectively.

Clinical illnesses

Nineteen patients have underlying diseases. The accompanying diseases were heart disease (atrial septal defect, Down syndrome with ventricular septal defect, Tetralogy of Fallot, total anomalous pulmonary venous return, and pulmonary stenosis with intact ventricular septum) in 5, malignancy (brain yolk sac tumor and acute myeloid leukemia) in 3, and chronic lung disease in 2. Others were biliary atresia with post-Kasai operation, chronic diarrhea, chronic granulomatous disease, Crouzon disease, Noonan syndrome, osteopetrosis, cerebral palsy, choroids plexus papilloma, and spinal muscular atrophy type 3. The other 20 patients were healthy children without any underlying disease. Three immunocompromised patients (one case of brain yolk sac tumor and 2 cases of acute myeloid leukemia) were identified and of older ages compared with others in this study group.

Their clinical illnesses were acute bronchiolitis/bronchopneumonia in 13, upper respiratory tract infection in 8, croup in 5, pharyngoconjunctival fever in 2, exudative tonsillitis in 2, herpangina in 2, hand-foot-mouth disease in 1, viral exanthem in 2, erythema multiforme in 1, newborn fever in 1, sepsis in 1, and febrile neutropenia in 1 leukemic patient.

It is worth mentioning that 2 patients were diagnosed as cases of pharyngoconjunctival fever due to prominently injected conjunctiva. Exudative tonsillitis was also observed in 2 patients. In one patient with exudative tonsillitis, both parainfluenza virus type 3 and adenovirus were isolated, while in the other 3, only parainfluenza virus type 3 was isolated.

Clinical manifestation

The most common clinical symptoms in all of the patients regardless of their clinical illnesses were (in the order of decreasing frequency) cough/productive cough, fever, rhinorrhea, poor appetite, hoarseness, and lethargy/decreased activity. Injected throat, shortness of breath/chest wall retraction, rales, wheeze, rhonchi, and stridor were the most prominent signs in terms of physical examinations in this series (Table 1).

Some patients presented with gastrointestinal symptoms, including nausea, vomiting, diarrhea, and abdominal pain. Five patients with skin rash had various clinical diagnoses and skin presentations. One was diagnosed as hand-foot-mouth disease with multiple oral ulcers and perianal papular skin lesion. One was diagnosed as possible pharyngoconjunctival fever with the manifestation of few petechiae and ecchymoses-like skin rash over the scapula and chest, combined with sore throat, prominently red throat and conjunctiva, nausea, and decreased appetite and activity. The other diagnoses were viral exanthem in 2 and erythema multiforme in 1 with the typical skin lesions. Parainfluenza virus type 3 was isolated from the above 4 cases with skin findings and parainfluenza virus type 2 in 1 patient with viral exanthem. However, no other concomitant virus was isolated in the above 5 cases with skin presentations.

Table 1. Clinical presentations of parainfluenza viruses infection (n = 39)

Symptom/sign	No. of cases (%)
Cough[a]/productive cough	32 (82.1)
Fever	30 (76.9)
Rhinorrhea	10 (25.6)
Poor appetite	8 (20.5)
Hoarseness	7 (17.9)
Skin rash	5 (12.8)
Diarrhea	4 (10.3)
Lethargy/decrease activity	4 (10.3)
Sore throat	4 (10.3)
Nausea/vomit	3 (7.7)
Abdominal pain	1 (2.6)
Injected throat	16 (41.0)
Short of breathless/chest wall retraction	14 (35.9)
Rales	14 (35.9)
Wheeze	12 (30.8)
Rhonchi	8 (20.5)
Stridor	8 (20.5)
Injected conjunctiva	3 (7.7)
Oral ulcer/vesicle	3 (7.7)
Tonsil with coating	2 (5.1)

[a]Barking cough was included.

Laboratory results

Laboratory tests were done in 31 cases, including hematogram and differential count, and C-reactive protein (CRP). Eight cases were not analyzed due to concurrent diseases, 3 of them were malignancy with febrile neutropenia. Five other cases were excluded because of sepsis and bacteremia (*Salmonella* sepsis, *Pseudomonas* sepsis, chronic diarrhea with *Salmonella* sepsis, osteopetrosis with port-A related sepsis, chronic granulomatous disease with *Aspergillus empyema*).

In the analyzed cases, initial white counts ranged from 3680 to 24 200 /mm^3. The initial white counts were as follows: 9 in 23 cases <10 000 /mm^3, 12 between 10 000 and 20 000 /mm^3, and 2 more than 20 000 /mm^3. CRP levels were available in 30 patients. Eight cases were not analyzed due to concurrent disease as mentioned above. The initial levels of CRP were greater than 1 mg/dL in 7 cases (7/22). The CRP levels ranged from 1.08 to 6.39 mg/dL in this series.

Discussion

Although parainfluenza viruses are considered common childhood pathogens, there has been a dearth of information on parainfluenza viruses in Taiwan. This study is important in terms of either clinical or epidemiologic considerations. Most of the infected patients were young children and no seasonal peak was observed in this study. The age distribution of this study paralleled those seen in previous foreign literature [2, 3,16,17]. However, parainfluenza viruses tend to occur with seasonal clustering, which was not observed in parainfluenza virus types 1 and 2 infections in this study. Inadequate case numbers may be a reasonable explanation. However, this study did observe an endemicity of parainfluenza virus type 3 infections in late spring of 2000 (Fig. 1).

This study revealed infants and young children were the major susceptible population and those younger than 3 years accounted for the majority (87.2%) of cases. Among the 3 types of parainfluenza viruses, parainfluenza type 1 viral isolates accounted for all cases of croup. Croup was diagnosed in 5 among 6 patients infected by parainfluenza virus type 1. In the 2 patients affected by parainfluenza virus type 2, one is respiratory tract infection following bone marrow

transplantation and the other one was viral exanthem. The majority of parainfluenza virus type 3 infections in this series were upper respiratory tract with or without involvement of the lower respiratory tract.

Previous experience has shown a certain degree of association between parainfluenza virus types 2 and 3 infections, and dermatologic findings in early childhood, such as maculopapular exanthem [18,19]. This study observed quite a number of cases of maculopapular rash with or without respiratory symptoms. Of particular interest was the identification of one case of erythema multiforme. In this case, the diagnosis of erythema multiforme was made based on the typical skin lesions and virological culture yielded parainfluenza virus type 3. Hence, parainfluenza virus infection may manifest as various kinds of skin lesions from simple viral exanthem to erythema multiforme. The pathogenesis of skin involvement needs further study to clarify even though the chances of a causal relation between parainfluenza virus infection and skin symptoms were formerly though to be slight.

Some other interesting cases also were identified from this study. Three cases were found to have clinical manifestations similar to herpangina and hand-foot-mouth disease. Two cases were suffering from illness reminiscent of pharyngoconjunctival fever. However, only an incidental connection is likely to exist between the clinical diagnosis and the parainfluenza virus infection. Hence, no other virus was isolated from the above concomitant specimens. Our findings raised the possibility of parainfluenza virus in causing the diseases typically thought to be caused by adenovirus or enterovirus.

Parainfluenza virus infection is usually asymptomatic or a self-limiting upper respiratory illness in healthy adults. In one series to determine the frequency of specific virus infections associated with acute respiratory tract conditions leading to hospitalization of chronically ill patients, influenza, parainfluenza, and respiratory syncytial virus infections accounted for 75% of all viral infections [8]. It highlighted the impact of parainfluenza viruses on individuals with chronic underlying conditions, especially chronic pulmonary conditions [8]. In immunocompromised patients, the severity of clinical illness depends on the type of virus and the type and degree of immunosuppression. One study have demonstrated that a minimum of 31% of adult bone marrow transplant recipients who are hospitalized with an acute respiratory illness have a community respiratory viral infection [20]. It documented that parainfluenza viruses accounted for 9% of all community respiratory infections confirmed by culture [20]. In the present series, interestingly, the 3 older patients were immunocompromised hosts with cancer. All the parainfluenza infections occurred during their neutropenic stage and were minor, without grave consequences.

In conclusion, parainfluenza viruses affected mostly young children, and accounted for a substantial morbidity in either outpatients or hospitalized patients. The clinical manifestations ranged from mild respiratory illness to bronchiolitis and pneumonia. A substantial proportion of patients in this study developed skin involvement. The identification of parainfluenza virus in illnesses classically thought to be caused by other viruses is intriguing and may have important implications in the management of childhood illness clinically.

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