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Epidemiological and Clinical Characteristics of Human Parainfluenza Virus Infection in Children of Xianyang Children's Hospital in 2022

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Data Article

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ABSTRACT

The incidence of HPIV infection in children is on the rise, particularly following the emergence of SARS-CoV-2, which presents a potential risk to the health of children.
Objective: This study aims to investigate the epidemiological and clinical features of human parainfluenza virus (HPIV) in children admitted to Xianyang Children's Hospital (Xianyang Caihong Hospital) from January 2022 to December 2022.

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Methods: Out of the 5873 cases of hospitalised children, the ones which had HPIV as the only pathogen and were non-standard cases were excluded, and the rest were analysed for their clinical characteristics, based on the six nucleic acids kits used to detect HPIV in respiratory tract viruses.
Results: Among 5873 cases of Nasopharyngeal swab specimens, there were 795 cases of HPIV antigen positive, of which 794 cases of HPIV3（13.52%, 3 cases of HPIV1（0.05%; There were 472 males (13.92%) and 325 females (13.09%) in them($\chi 2$ =0.381, *P*=0.362).The infection rates in spring, summer, autumn and winter were 8.03%, 55.71%, 28.48% and 7.78%, respectively, and the difference of pairwise comparison were statistically significant ($\chi 2$=539.158, *P*=0).There were 318 cases (19.51%) in infant group and 164 cases (10.86%) in children group ($\chi 2$=45.118, *P*=0). With HPIV as the sole pathogen including 363 cases of bronchopneumonia, 237 cases of bronchitis, 8 cases of pertussis syndrome, 84 cases of bronchiolitis.
Conclusion: (1). During the period of January to December 2022, Xianyang Children's Hospital has seen a high prevalence of HPIV, a virus causing lower respiratory tract infection, especially HPIV3. (2).No statistical evidence showed a difference between men and women in terms of high morbidity during spring and summer, which was more common among infants and young children. (3). Among children infected with HPIV, the four most common respiratory illnesses are bronchopneumonia, bronchitis, pertussis syndrome, and bronchiolitis. After undergoing symptomatic treatment, most children showed marked improvement. It is imperative to gain a thorough understanding of HPIV infections in children, enabling timely prevention and symptomatic treatment, identifying critical and serious illnesses, and reducing morbidity and mortality.

Keywords: HPIV; children; manifestation; treatment.

1. INTRODUCTION

Chanock et al. firstly reported the isolation of Human parainfluenza viruses (HPIVs) from children with croup in 1956 [1]. HPIVs are enveloped, single-stranded RNA viruses that are part of the paramyxoviridae family, which includes HMPV and RSV. There are four types of HPIVs based on genetic and antigenic differences, labeled as 1, 2, 3, and 4, with two subtypes, 4a and 4b. HPIV-1 and HPIV-3 are classified as Respiroviruses, while HPIV-2 and HPIV-4 are Rubulaviruses [2].

HPIVs are a common respiratory pathogen, affecting people of all ages, genders, races, and socioeconomic backgrounds, without geographic limitation. The clinical manifestations of HPIVs are varied, including croup, asthma, cough, rhinorrhea, sore throat, bronchiolitis, and pneumonia (with or without fever) [3]. Children, the elderly, and those with weakened immune systems who contract HPIVs can experience serious LRTIs. It is the second most common virus, after RSV, to cause acute respiratory tract infections in children under 5 [4].

This study seeks to investigate the positive rate, epidemiological characteristics, and clinical manifestations of HPIVs in acute respiratory infections (ARIs) in Xianyang from January 2022 to December 2022 retrospectively, with the purpose of understanding the epidemiological characteristics of HPIVs in Xianyang and providing epidemiological evidence for the prevention and control of HPIVs infection in Xianyang.

2. MATERIALS AND METHODS

2.1 Materials

Between January 2022 and December 2022, the Children's Hospital of Xianyang enrolled 5873 inpatients, with 3391 males and 2482 females.Across all age groups from 0-18 years, with 1423 cases aged < 1 year, 1630 cases aged 1-3 years, 1510 cases aged 3-5 years, and 1310 cases aged ≥5 years. During the four seasons, spring (March, April and May) had 64 cases, summer (June, July and August) had 444 cases, autumn (September, October and November) had 227 cases and winter (December, January and February) had 62 cases.

2.2 Methods

2.2.1 Respiratory sample collection

Gently insert the swab into the nasopharynx, just above the bottom of the nasal passage, along the palate until resistance is felt. If you encounter any resistance, try to reinsert it at a different angle, leaving the swab in place for a few

seconds to absorb the discharges, then slowly rotate and remove it. After that, open the collection tube and insert it. All procedures should be done in accordance with the New England Journal of Medicine's guidelines [5].

2.2.2 Real-time polymerase chain reaction (PCR) for detection of HPIV and other common respiratory pathogens

Samples from the respiratory system were extracted for DNA or RNA using the QIAamp DNA Mini Kit or QIAamp Viral RNA Mini Kit (QIAamp Co., Shanghai, China) as per the manufacturer's instructions. TaqMan real-time PCR was used to detect two HPIV viruses (HPIV1 and HPIV3) and four other common respiratory pathogens, such as influenza A virus (IAV), influenza B virus (IBV), respiratory syncytial virus (RSV), and adenovirus (ADV).

2.3 Statistic Analysis

SPSS 26.0 statistical software was utilized for the analysis of the count data, which were expressed as percentages or rates. The chi-square test was employed for comparison, with the test level set at $\alpha=0.05$. To adjust for multiple comparisons, the test level was adjusted to $\alpha=0.008$.

3. RESULTS

3.1 Epidemiological Characteristics of HPIV

3.1.1 Results of pathogen detection

Among the 5873 respiratory virus nucleic acid samples, 797 cases were positive for HPIV, the detection rate was 13.5%, the detection rate of HPIV1 was 0.05% (3/5873), the detection rate of HPIV3 was 13.52% (794/5873), and the positive rate of HPIV3 was 99.62% (794/797). The positive results of HPIV combined with other pathogens are shown in Table 1.

Table 1, RSV, Respiratory syncytial virus; ADV, Adenovirus; IBV, influenza B virus; EBV, Epstein-Barr virus; CMV, Cytomegalovirus; BP, Bordetella pertussis; SP, Streptococcus pneumoniae; SA, Staphylococcus aureus; EV, Enterovirus; CA, Coxsackievirus; CVB, Coxsackievirus B; MP, Mycoplasma pneumoniae; HV, Hantavirus.

3.1.2 The gender-based profile of HPIV infection

The individuals affected by HPIV, 472 were male (472/3391) and 325 were female (325/2483). This gave a male to female ratio of 1.45:1, which was not statistically significant ($\chi2=0.381$, $P=0.362$). Further information can be found in Table 2.

3.1.3 Age characteristics of HPIV infection

There were 256 children under 1 year old, making up 32.12% of the total number of positive cases. The infection rate of each age group, from highest to lowest, was 1-3 years old, < 1 year old, 3-5 years old, and ≥5 years old, and the difference in the ratio of each group was statistically significant ($\chi2=173.997$, $P=0.000$). There was no significant difference between the < 1 year old group and the 1-3 years old group, while the differences in the other groups were statistically significant. See Table 3.

Table 1. HPIV coinfection with other pathogens

Pathogens	Cases	Pathogens	Cases
RSV	17	SP	75
ADV	26	SA	35
IBV	7	EV-IgM	28
EBV-DNA	47	CA-16-IgM	10
CMV-DNA	44	CVB-IgM	12
CMV-IgM	2	MP-DNA	4
BP-DNA	8	MP-IgM	3
EV71-IgM	6	HV-IgM	1

Table 2. The gender distribution of HPIV infection

Gender	HPIV1	HPIV3	HPIV	Total	Ratio（%）
Male	2	470	472	3391	13.92
Female	1	324	325	2482	13.09

Table 3. Age characteristics of HPIV infection

Age(year)	HPIV1	HPIV3	HPIV	Total	Ratio（%）
＜1	1	255	256	1423	17.99
1-3	1	317	318	1630	19.51
3-5	1	163	164	1510	10.86
＞5	0	59	59	1310	4.50

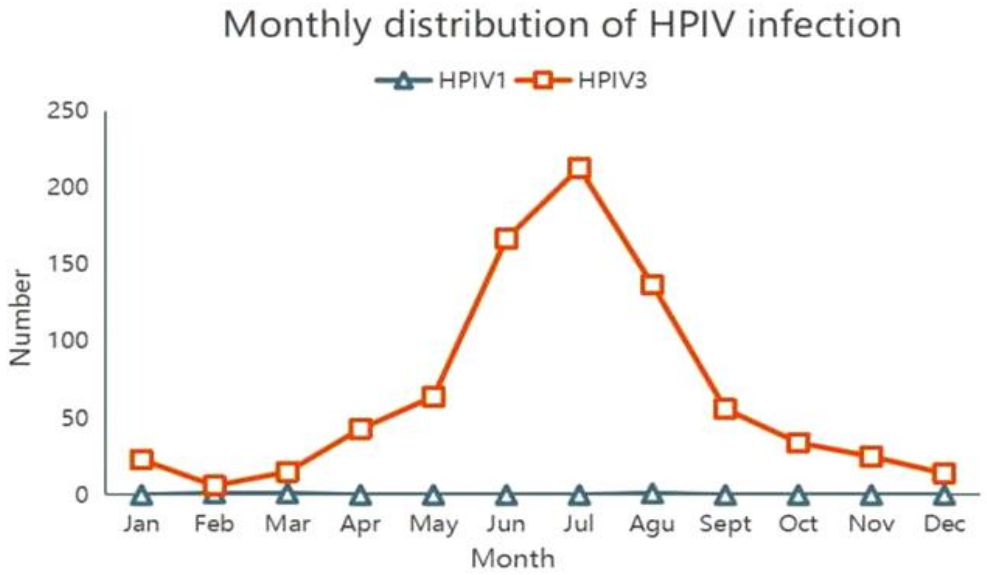

Fig. 1. Monthly distribution of HPIV infection

3.1.4 Seasonal distribution of HPIV infection

HPIV1 and HPIV3 were both detected throughout the year, with the highest prevalence in spring and summer. HPIV1 had its peak in April, May and June, while HPIV3 had its peak in May, June and July, and was relatively rare in winter. According to the data, there were 64 cases in spring, 444 cases in summer, 227 cases in autumn and 62 cases in winter. The infection rates in spring, summer, autumn and winter were 8.03%, 55.71%, 28.48% and 7.78%, respectively, and the difference in the four seasons was statistically significant ($\chi2$=539.158, *P*=0.000). Additionally, the chi-square segmentation method showed that the pairwise comparison of each quarter was statistically significant (spring and summer $\chi2$ =91.268, *P*=0.000; spring and autumn $\chi2$=0.258, *P*=0.612; spring and winter $\chi2$=47.219, *P*=0.000; summer and autumn $\chi2$=198.407, *P*=0.000; summer and winter $\chi2$=453.282, *P*=0.000; autumn and winter $\chi2$=85.213, *P*=0.000).

3.2 Clinical Characteristics of HPIV Infection

3.2.1 Criteria for inclusion

Among the hospitalized children in our hospital in 2022, the pathogen detection was HPIV and accompanied by clinical symptoms. With the criteria for HPIV co-infection being a positive nucleic acid test or serum antibody IgM, including Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia trachomatis, pertussis. A total of 5873 cases were screened, including 3 cases of HPIV1 positive and 794 cases of HPIV3 positive. The clinical manifestations, laboratory

tests, imaging examinations and diagnosis were collected and statistically analyzed.

3.2.2 Criteria for exclusion

The patient was discharged without recovery and the guardian of the child declined to take part in the study. Moreover, individuals who had concomitant inherited metabolic diseases or serious organ failure were not eligible for this study.

3.2.3 Symptoms and signs

Among the 797 cases (475 cases were only infected by HPIV), 526 cases (65.99%) had fever. The duration of fever ranged from transient fever to 7 days, mostly 1-3 days. The average thermal peak was (38.69±0.62) ℃, and 388 cases had moderate to low fever. There were 712 cases of paroxysmal cough (89.34%), 8 cases of spastic cough. Wheezing occurred in 88 cases (11.04%). 112 cases (23.58%) had gastrointestinal reaction, other symptoms and signs.including nasal obstruction, runny nose, Swollen tonsils, wheezing, dyspnea.See Table 4.

3.2.4 Laboratory tests

The white blood cell count ranged from (1.41-38.85)×10^9/L, with an average of (9.62 ± 4.58)×10^9/L. Twenty-four cases had a count of less than 4×10^9/L, while 25 cases had a count of more than 20×10^9/L. Without receiving any antibiotic treatment, 246 cases showed improvement after admission. It was not possible to rule out the possibility of increased white blood cells in the early stages of viral infection or the influence of glucocorticoids before admission. Hemoglobin levels were between (74 - 217) g/L, with an average of (120.77 ± 11.95) g/L. Twenty cases had a platelet count of more than 600 ×10^9/L. Results from the laboratory tests such as C-reactive protein, alanine transaminase, and creatine kinase-MB are presented in Table 5.

Table 4. Symptoms and signs of HPIV infection

Symptom	Cases	Ratio（%）
Fever	324	68.21
Cough	413	86.95
Nasal congestion	178	37.47
Runny nose	180	37.89
Swollen tonsils	198	41.68
Gastrointestinal symptoms	112	23.58
Wheezing	52	10.95
Dyspnea	8	1.68

Table 5. Outcome from the laboratory test

Idex	Range	$\bar{x}\pm S$	Abnormal	Trend (↑/↓)	Ratio（%）
WBC	1.41-38.85	9.62±4.58	299	↑	37.90
NEU	0.11-26.26	4.59±3.82	228	↓	29.16
LYM	0.21-18.74	3.73±2.09	403	↑	51.73
RBC	1.45-6.55	4.58±0.45	156	↓	20.13
HGB	74-217	120.77±11.95	624	↓	79.90
PLT	115-751	315.17±113.14	247	↑	31.42
CRP	0-183.5	14.35±26.98	293	↑	37.47
hs-CRP	0-200.8	15.78±28.81	379	↑	49.93
SAA	0-499.7	79.29±106.64	459	↑	59.07
PCT	0-42	0.51±1.89	141	↑	18.15
ESR	1-222	14.96±16.88	149	↑	19.20
PA	48-389	163.93±45.27	628	↓	90.75
LDH	68-673	309.53±62.45	673	↑	93.86
HBDH	22-811	168.58±99.67	157	↑	20.31
CK-MB	0-497	25.21±26.07	224	↑	41.25
IgM	0.06-6	1.0.±0.52	14	↓	2.58
IgA	0.05-7.55	0.77±0.67	151	↓	27.91
IgG	0.21-19.04	6.48±2.44	181	↓	25.97

Table 6. Hospital stay of the patient

Hospital stay	＜3d	3-5d	5-10d	＞10d
Cases	55	288	396	58

3.2.5 Classification of diseases

Out of the 797 cases, 363 were diagnosed with bronchopneumonia, of which 1 was caused by HPIV1 and 362 by HPIV3. Additionally, 237 cases of bronchitis were reported, 2 of which were caused by HPIV1 and 235 by HPIV3. 8 cases of pertussis syndrome were attributed to HPIV3, as well as 5 cases of bronchiolitis. 32 cases of acute laryngitis were also caused by HPIV3, as well as 121 cases of upper respiratory tract infection, 9 cases of severe pneumonia, and 10 cases of respiratory failure. Lastly, 2 cases of viral encephalitis, 5 cases of benign myositis in children, and 14 cases of mild gastroenteritis with benign infantile convulsion were all attributed to HPIV3.

3.2.6 Treatment and outcome

Among the 797 cases, 246 cases did not receive antibiotics and tracheal intubation, 44 were treated with intravenous glucocorticoids for inflammation and asthma prevention, 2 cases received intravenous human gamma globulin, and the rest were given back patting, sputum suction, atomizing inhalation, and other symptomatic treatments. The average hospital stay was (6.31±2.49) days, ranging from 2-20 days (Table 6). All cases improved and were discharged after treatment.Hospital costs ranged from 942.18 to 20498.16 yuan, with an average of 4657.61 yuan and a standard deviation of 2490.99.

4. DISCUSSION

HPIV has been linked to respiratory illnesses in both children and adults, with the clinical signs of PIV infection in adults being less predictable and the pathogen sometimes going unnoticed due to its similarity to other respiratory illnesses [6]. Common illnesses associated with HPIV include otitis media, pharyngitis, conjunctivitis, hip joint inflammation, tracheobronchitis, and pneumonia. Additionally, rare respiratory conditions such as apnea, bradycardia, mumps, and respiratory distress syndrome have been reported. Although HPIV primarily affects the respiratory system, it can also cause illnesses in other organs, including the nervous system, kidneys, and rheumatic diseases [1]. HPIV infection can present asymptomatically, or with mild symptoms of the upper and lower respiratory tract, with infants and young children more likely to experience more severe symptoms [7]. In children, between 40-60% of HPIV infections cause URTIs (colds and pharyngitis), with around 30-50% of these illnesses accompanied by otitis media. URTI is the most common symptom of all serotypes, and fewer than 20% of HPIV infections lead to LRTI [1].

In Xianyang Children's Hospital, HPIV is a major virus responsible for ARIs in infants and young children, and this was established via multiple reverse transcription-polymerase chain reaction in 2022. Moreover, it was found that HPIV3 was the dominant type among HPIV1/3, with the significance of $P < 0.01$. This finding is consistent with other studies conducted in Japan, Thailand, Central and South America and other parts of the world, which revealed that HPIV3 is the principal pathogen in HPIV [8-9]. It is not uncommon for HPIV to be associated with other pathogens, e.g. RSV, CMV, EBV and bacteria, which can be attributed to the weakened immunity of individuals caused by viral infection during the epidemic season. The virus can invade the respiratory tract, damaging the mucosa and increasing the risk of bacterial infection. Reports have shown that 18-65% of ARI patients have HPIV coinfection. Co-infection seems to be connected to the prolonged presence of the virus in the respiratory mucosa. The co-infection rate of the virus in infants and young children is notably higher than that of older children and adults. There was no distinction in HPIV infection between males and females [10].

Young children had the highest rate of infection, with no major distinction between the infant group and the young children group. This research demonstrated that HPIV3 infection was prevalent in spring and summer in Xianyang, which was in agreement with the findings of Wenzhou, Qindao, and Beijing in China [11-13], as well as countries such as the United States (in the south), Finland, Korea and Australia [14-17]. Studies in Guangzhou have indicated that the infection peaks of HPIV1 and HPIV3 occur in late autumn and early winter, and late summer and early autumn respectively, with the peak of HPIV1 occurring earlier than HPIV3 [18].

Coughing is the primary indication of HPIV infection, and spasmodic coughing is more frequent in infants, which is in line with the findings of the Capital Institute of Pediatrics [19]. Signs and symptoms such as fever, wheezing, moist rales and wheezing in the lungs are commonly seen in patients infected with HPIV, with a few experiencing convulsions and gastrointestinal reactions. Generally, the laboratory and chest imaging results are not severe. The most common respiratory diseases associated with HPIV include bronchopneumonia, bronchitis, pertussis syndrome and bronchiolitis [20]. HPIV1 infection was most likely to cause bronchopneumonia, with acute laryngitis, bronchitis, and upper respiratory tract infection following [21]. Bronchopneumonia was the most frequent HPIV3 infection, followed by pertussis syndrome, bronchitis, and bronchiolitis. The causative agent of pertussis syndrome was HPIV3. Only two cases of severe pneumonia were reported, one of which was associated with moderate malnutrition [22].

Children with HPIV infection had a prolonged course of illness, with 58 cases (7.35%) lasting more than two weeks, 8 cases (1.00%) lasting over a month, and the longest course of disease being two months. Upon admission to the hospital, the children presented with a two-month-long cough and wheezing. It is worth noting that 105 cases had been treated with antibiotics prior to admission, with the course of treatment ranging from one to sixteen days, and 62 cases had no effect or even worsened. After admission, 59.70% of the cases did not require antibiotics. One patients who were clinically diagnosed with pertussis syndrome (with no other causative bacteria except HPIV infection) were treated with azithromycin, indicating that overuse of antibiotics is still a problem in children with HPIV infection. Rapid and highly sensitive tests such as seven respiratory viruses and PCR can help to identify the etiology and reduce the inappropriate use of antibiotics.

To sum up, HPIV is a frequent cause of respiratory tract infection among hospitalized children in our hospital. In 2016, HPIV3 was the most prevalent, often accompanied by other pathogens, mainly causing bronchopneumonia, bronchitis, pertussis syndrome, and bronchiolitis. The majority of the symptoms were not severe, and the duration of the illness was slightly longer. To mitigate the transmission of COVID-19 and other respiratory illnesses, social distancing has been implemented to a certain degree. Unfortunately, reducing these safety protocols has caused a resurgence of viruses like HPIV 3 during the pandemic [23-25].Administering symptomatic treatment can help the condition to improve gradually.

5. CONCLUSION

No vaccine has been developed to stop HPIV infection, and no medications approved by the government are available to treat it [3]. Further efficacy trials are required to assess the effectiveness of two vaccines in preventing PIV3 disease and in providing a model of protection against respiratory illness through mucosal vaccination. These two vaccines are the Intranasally administered bovine PIV3 vaccine and the cold-adapted PIV3 vaccine [26]. Antiviral treatments are essential to reduce the severity and mortality related to HPIV diseases. Hemagglutinin neuraminidase (HN) is one of the two HPIV outer proteins which plays a major role in the detection, adhesion, and cleavage of the host. Scientists have developed various HN inhibitors to battle HPIV, but only one host-targeted therapy (DAS181) has been tested in phase II clinical tests and proven successful [27]. DAS181 is a novel sialidase fusion protein that eliminates sialidase-containing receptors from the surface of respiratory epithelial cells, thus obstructing PIV and influenza virus from attaching to these cells. Additionally, DAS181 has been demonstrated to have in vitro and in vivo activity against PIV. It has been observed to be beneficial in the treatment of immunocompromised children with moderate respiratory distress due to PIV infection. In adults, DAS181 has been used to treat PIV infection and pneumonia in hematopoietic stem cell transplant recipients and lung transplant recipients [28].

Pediatricians should be aware of the critical and severe cases of HPIV infection, as it can be life-threatening and require IVIG or glucocorticoids treatment. Apart from symptomatic treatment, DAS181 may be the most promising drug for future clinical application.

CONSENT AND ETHICAL APPROVAL

The Xianyang Children's Hospital Ethics Committee (XCHE2021086) has been presented with the study for approval. In addition to a paper outlining the research, verbal information is also given. Before any patient was included in the

study, the parent or legal guardian of the patient had to sign a consent form.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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